

Evidence Synthesis

Number 148

Screening for Preeclampsia: A Systematic Evidence Review for the U.S. Preventive Services Task Force

Prepared for:

Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. HHSA-290-2012-00151-I, Task Order No. 4

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AHRQ Publication No. 14-05211-EF-1

April 2017

This report is based on research conducted by the Kaiser Permanente Research Affiliates Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHS-2012-00151-I, Task Order No. 4). The findings and conclusions in this document are those of the authors, who are responsible for its contents, and do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this report: Iris Mabry-Hernandez, MD, MPH, at AHRQ; current and former members of the U.S. Preventive Services Task Force who contributed to topic deliberations; Aaron B. Caughey, MD, PhD, Liona Poon, MBBS, MRCOG, MD(Res), and James M. Roberts, MD, who provided expert review; the National Institute of Child Health and Human Development, the U.S. Department of Veterans Affairs, and the Indian Health Service, who provided federal partner review; and Smyth Lai, MLS, Elizabeth Hess, ELS(D), Elizabeth O'Connor, PhD, Ning Smith, PhD, and Maya G. Rowland, MPH, at the Kaiser Permanente Center for Health Research.

Suggested Citation

Henderson JT, Thompson JH, Burda BU, Cantor A, Beil T, Whitlock EP. Screening for Preeclampsia: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 148. AHRQ Publication No. 14-05211-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2017.

Structured Abstract

Background: The U.S. Preventive Services Task Force (USPSTF) does not currently have an active recommendation for preeclampsia screening. Preeclampsia is a complex disease occurring in the second half of pregnancy, and is estimated to affect nearly 4 percent of pregnancies in the United States. Nearly 9 percent of maternal deaths in the United States are directly attributed to preeclampsia and eclampsia, and it is a leading cause of induced preterm birth and low birth weight. Early detection through general or high-risk screening approaches may help reduce the health-related consequences, particularly for infants.

Purpose: We conducted a systematic review to assess the direct evidence of benefits and harms of preeclampsia screening on health outcomes; to evaluate the effectiveness of routine blood pressure and urine protein screening tests to identify women with preeclampsia; to estimate the accuracy of screening tests for proteinuria; and to evaluate the performance of multivariable risk assessment tools used during the first trimester to identify women at increased risk of preeclampsia as well as the potential harms of risk assessment.

Data Source: MEDLINE, PubMed, and Cochrane Central Register of Controlled Trials from 1990 through September 1, 2015. We included all references from the 1996 USPSTF recommendation and examined reference lists of relevant systematic reviews.

Study Selection: English-language trials and observational studies of screening effectiveness, test accuracy, and harms. Two investigators independently reviewed identified abstracts and full-text articles against a set of a priori inclusion and quality criteria.

Data Analysis: One investigator abstracted details about study design, patient population, setting, screening method, followup, and results. Two investigators independently applied prespecified criteria to rate study quality. Discrepancies were resolved through consensus, and poor-quality studies were excluded. Due to small numbers of studies and methodological shortcomings, meta-analysis was not attempted for any outcome measure other than urine protein:creatinine tests performed as point-of-care screening.

Results: A fair-quality randomized, controlled trial of 2,764 “low-risk” pregnant U.S. women found no statistically significant differences in health outcomes among women assigned to fewer prenatal screening visits compared with usual care at a large managed care organization in 1996 (mean number of visits, 12.0 vs. 14.7; $p < 0.001$). A fair-quality before-after study of 1,952 low-income pregnant Hispanic women did not identify harms related to preeclampsia diagnosis and birth outcomes when protein urine screening was used for specific indications instead of on a routine basis in prenatal care. We found no evidence to evaluate the effectiveness of routine screening tests in identifying women with preeclampsia and limited evidence on various screening approaches for establishing the presence of proteinuria (a diagnostic criterion for preeclampsia). Fourteen diagnostic test accuracy studies (four good-quality, 10 fair-quality) compared point-of-care tests used to screen for proteinuria versus the gold standard (24-hour urine collection). Included studies of test accuracy were conducted in women with suspected preeclampsia, while studies with healthy, asymptomatic patients seeking routine care were

lacking. Twelve studies evaluated the performance of protein:creatinine tests. High heterogeneity precluded pooling of test performance ($k=11$). Sensitivity for the protein:creatinine test ranged from 0.65 to 0.96 ($I^2=80.5\%$; 11 studies) and specificity ranged from 0.49 to 1.00 ($I^2=91.8\%$; 11 studies). Statistical heterogeneity of test sensitivity was partly explained by differences in the study populations; studies with a positive protein dipstick result as an inclusion criterion had higher sensitivity ($p<0.05$). Two studies of the albumin:creatinine spot test had high sensitivity (≥ 0.94 , [95% confidence interval, 0.75 to 1.00]). Four studies of quantitatively read protein dipstick tests had widely variable sensitivity (0.22 to 1.00) and specificity (0.36 to 1.00). Four studies validated five first-trimester risk assessment models with good-to-excellent discrimination, primarily for predicting early-onset preeclampsia requiring delivery. No externally validated multivariable risk prediction models were based only on patient history measures that could be collected in a routine prenatal care visit; all included serum markers and uterine artery Doppler ultrasound measure of the pulsatility index, or both. Five models had good discrimination of preeclampsia cases (c -statistic, >0.80) but very low positive predictive values and did not provide necessary information on model calibration.

Conclusions: Changes in diagnostic criteria, patient demographics, and treatment recommendations affect the applicability of previous trials, precluding conclusions about the optimal screening approach. Most studies for detecting proteinuria, one of the diagnostic criteria for preeclampsia, tested the protein:creatinine ratio in urine samples; however, all studies were among patients with prescreened suspicion of preeclampsia and none evaluated the performance of repeat testing of urine protein for screening. Due to limited and variable evidence, different urine protein screening tests cannot be compared. There was no clear evidence of the performance, clinical benefits, or harms of any externally validated models for risk prediction, and the clinical performance and impact of risk prediction models could not be extrapolated to relevant patient settings. Current screening practices are considered routine and represent relatively minor burdens to patients, clinicians, and health care systems, but evidence is limited for determining the benefits and harms of preeclampsia screening.

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Chapter 1. Introduction

Condition Definition

Preeclampsia is a multisystem syndrome that is primarily defined by the development of new-onset hypertension, persistent systolic blood pressure [SBP] of 140 mm Hg or higher, or diastolic blood pressure [DBP] of 90 mm Hg or higher after 20 weeks' gestation in a woman with previously normal blood pressure.¹ Although preeclampsia is usually accompanied by new-onset proteinuria, the American Congress of Obstetrics and Gynecology (ACOG) recently revised the diagnostic criteria for preeclampsia so that the presence of proteinuria for diagnosis was no longer required, noting that elevated blood pressure accompanied by other signs and symptoms is sufficient for diagnosis. These other signs are also included in new terminology proposed by ACOG to identify cases with severe features. Those severe features are: very high blood pressure, thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, and cerebral or visual symptoms. The proportion of women who develop preeclampsia without proteinuria or who have proteinuria without hypertension preceding preeclampsia is unclear, with inconsistent definitions and approaches to measurement, and few studies examining these atypical presentations.^{2,3} Proteinuria levels among women diagnosed with preeclampsia, however, are not found to be consistently associated with adverse outcomes.^{4,5}

Systems for diagnosing and classifying the severity of disease vary across professional societies and organizations, including ACOG, the American Society of Hypertension, and obstetrics and gynecology professional organizations in the United Kingdom, Canada, New Zealand, and Australia. Fetal complications of preeclampsia include intrauterine growth restriction (IUGR) and can occur due to placental perfusion problems. Preeclampsia often remains stable until delivery but sometimes can rapidly and unpredictably take a more serious turn. Severe hypertension, eclampsia, or HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet counts) and organ and systemic complications can lead to maternal or fetal injury and death.^{6,7} For this reason, the term “mild preeclampsia” has been recommended against in the new ACOG diagnostic criteria.

Other hypertensive conditions overlap and can coexist with preeclampsia. Chronic hypertension is defined as predating the pregnancy and/or continuing beyond 12 weeks postpartum. Women with chronic hypertension are diagnosed with superimposed preeclampsia if proteinuria develops after 20 weeks' gestation. Pregnant women who develop hypertension during pregnancy (without proteinuria) that subsides within 12 weeks postpartum are defined as having gestational hypertension.

The concepts of early- and late-onset preeclampsia have been used to define different manifestations of the syndrome and may reflect differences in pathophysiology as well as long-term outcomes. These timing categories usually distinguish between cases developing prior to 34 weeks' gestation versus later in pregnancy.⁸ Early-onset preeclampsia is associated with more severe maternal and fetal outcomes and may be especially influenced by aberrations in the placentation process, particularly in the remodeling of the maternal uterine spiral arteries.^{8,9} Later-onset disease may also involve placental dysfunction, but it often occurs in women with

proinflammatory maternal constitutional and environmental factors, such as multiple gestation, high body mass index (BMI), comorbid conditions, and chronic hypertension. Although pathophysiologic markers and processes underlying the development of preeclampsia are becoming more clearly understood, there remain considerable gaps in science that confer challenges for diagnosis and treatment.¹⁰

Prevalence and Burden of Preeclampsia

Approximately 2 to 8 percent of pregnancies are affected by preeclampsia, which is the second leading cause of maternal mortality worldwide.^{11,12} In the United States, the rate of preeclampsia increased from 3.4 percent in 1980 to 3.8 percent in 2010,¹³ and was accompanied by a rise in severe cases, which increased from 0.3 percent in 1980 to 1.4 percent in 2010.

Based on the most recent analysis of the Centers for Disease Control and Prevention Pregnancy Mortality Surveillance System data, 9 percent of maternal deaths are directly attributed to preeclampsia and eclampsia.¹⁴ Complications of preeclampsia also indirectly contribute to approximately 1 in 10 pregnancy-related deaths attributed to anesthesia, cardiomyopathy, or placental abruption.¹⁵ Serious morbidity is far more common than mortality; it has been estimated that more than one third of severe obstetric morbidities are related to preeclampsia.¹⁶ Significant maternal morbidities include cerebrovascular bleeding, retinal detachment, and complications from HELLP syndrome, such as major organ damage and failure.⁸ Eclampsia occurs in approximately 1 to 2 percent of preeclampsia cases, with complications such as brain damage, aspiration pneumonia, pulmonary edema, placental abruption, disseminated coagulopathy, acute renal failure, cardiopulmonary arrest, and coma.¹² Cohort data from obstetric patients attending 25 U.S. medical centers comprising the Maternal-Fetal Medicine Units Network in 2008 to 2011 indicated that at least 21 percent of severe maternal morbidity was related to hypertension-related complications.¹⁷ The prevalence of hospitalizations from severe preeclampsia or eclampsia rose from 9.4 to 12.4 per 1,000 deliveries in the United States between 1998 and 2006,¹⁸ and there is some recent indication that hospitalizations due to eclampsia may be falling.¹⁹

Preeclampsia also dramatically increases risks to the fetus or neonate. These risks include IUGR, small for gestational age (SGA), low birth weight, premature birth, oligohydramnios, placental abruption, low Apgar score, neonatal intensive care unit admission, stillbirth, and neonatal death.^{6,20} Because the treatment for preeclampsia is delivery, it is a leading cause of induced preterm birth and low birth weight. It has been estimated that preeclampsia is an indication in 6 percent of preterm births and 19 percent of medically indicated preterm births.²¹ Infants born before term (<37 weeks' gestation) are at increased risk of morbidity and mortality, with risks rising dramatically with earlier delivery. When preeclampsia occurs before 34 weeks, maternal and perinatal risks are greater and management decisions have to balance maternal and perinatal health risks. The majority of preeclampsia cases occur after 34 weeks, but morbidity and mortality is greater for early-onset disease.²²

Obstetric interventions are more common in pregnancies complicated by preeclampsia, and can include induction of labor (preterm or term), intravenous magnesium sulfate treatment, and

emergency or planned cesarean delivery. Early delivery interventions can improve maternal health and reduce some risks to the neonate, such as stillbirth, while increasing others, depending on the severity of disease and gestational timing.^{23,24} There is evidence that preeclampsia itself is associated with poor psychosocial outcomes, posttraumatic stress syndrome, and postpartum depression,²⁵⁻²⁸ with fetal or neonatal morbidity or mortality contributing to but not entirely accounting for the relationship.

In the United States, the prevalence of preeclampsia reveals marked disparities by race/ethnicity.²⁹⁻³¹ The rate of pregnancy-related death is 4 times greater among non-Hispanic black women, and preeclampsia is a major contributor to this disparity.³² National data on chronic and gestational hypertension show the conditions are more common and increasing over time among non-Hispanic black women, least common among Asian/Pacific Islander and Hispanic women, and intermediate among non-Hispanic white women.³³ Case fatality rates for preeclampsia are 3 times higher among black non-Hispanic women than among white women, contributing to the large mortality disparity.³⁴ Approximately one third of the disparity in mortality from preeclampsia among black women stems from higher prevalence, and the remainder is due to a higher case fatality rate.³⁴ Disparities in risk factors for preeclampsia, such as chronic hypertension, diabetes, and high BMI, contribute to a higher prevalence of preeclampsia among black women, and disparities in access to adequate prenatal care decrease opportunities to intervene before preeclampsia becomes more severe.³⁵ Inadequate prenatal care is associated with higher case fatality rates for preeclampsia among all women, which is likely due to the reduced opportunity for monitoring, detection, and early intervention.^{15,32} Nevertheless, even in a large population (n=35,529) provided with early access to prenatal care, racial/ethnic disparities have been observed, with minority women experiencing higher rates of preeclampsia than non-Hispanic white women.³⁶ Finally, recurrent preeclampsia in subsequent pregnancies is often more severe for black women than for white or Hispanic women.³⁷

Etiology and Natural History

Preeclampsia is a complex disease with multiple causes and interactions leading to its clinical manifestation. Its intractability to effective treatment (apart from delivery of the placenta) makes it an area of considerable scientific inquiry with important implications for women's health worldwide. The heightened risk of preeclampsia in first pregnancies and in women who undergo in vitro fertilization with donor eggs have led to numerous investigations regarding a potential role of the immune system and paternal genetic influences.⁶ Preeclampsia is generally understood to be an immunologic and inflammatory condition that involves the process of placentation, but the underlying causes, precipitating factors, and conditions are not fully understood.

Preeclampsia may develop through different processes that can occur either alone or in combination. "Placental" disease may lead to earlier onset and more severe disease, while "maternal" disease may result in later-onset disease.^{7,8} Placental preeclampsia is thought to arise from problems with the process of placentation whereby trophoblast cells fail to fully activate transformation of uterine spiral arteries (at about 12 to 16 weeks' gestation), resulting in placental ischemia. This relative ischemia and lowered placental perfusion could cause the

release of damaging factors (e.g., cellular debris, oxidized lipids, antiangiogenic factors) into the maternal bloodstream, resulting in inflammation and oxidative stress. In contrast, maternal preeclampsia is thought to involve overactive inflammatory responses to normal placentation. Preexisting hypertension, diabetes, and other inflammatory conditions (e.g., lupus) as well as twin or higher-order pregnancies are thought to precipitate a systemic inflammatory response and oxidative stress process. Consistent with this theory, women with early-onset placental preeclampsia exhibit abnormal uterine artery ultrasound Doppler readings and placental morphology compared with women without preeclampsia or later-onset disease.^{7,8,38} Adding to the complexity, maternal and environmental factors may also contribute to the risk of developing placental preeclampsia.

Preeclampsia can occur without immediate apparent adverse health consequences for the mother or infant. Challenges in preventing and treating the disease are heightened by the difficulty in determining who will develop preeclampsia and go on to experience severe or life-threatening complications. Preeclampsia also may pose a longer-term risk factor for poor cardiovascular health in mothers and their offspring.³⁹ The association may be explained by common risk factors, and it is unclear whether or not preventing preeclampsia would benefit the long-term cardiovascular health of women or children of mothers with preeclampsia is the subject of ongoing inquiry.

Despite intensive research, understanding of this complex disease is not complete. Most recently, the possibility that preeclampsia is a syndrome comprised of multiple subtypes has been proposed to explain its diverse etiology and unpredictable course.^{40,41}

Risk Factors

There are a number of well-established clinical and historical risk factors for preeclampsia.⁴² Chronic health conditions with increasing prevalence in the United States, such as essential hypertension and diabetes, affect the risk for preeclampsia. Women with preexisting hypertension or new-onset hypertension in pregnancy are at elevated risk of developing preeclampsia.⁴³ A recent systematic review of more than 50 studies, including nearly 800,000 pregnancies, estimated the incidence of superimposed preeclampsia among women with chronic hypertension to be 26 percent (95% confidence interval [CI], 21% to 32%).⁴⁴ In pregnant women with preexisting diabetes, the incidence of preeclampsia increased from 18 percent in women without preexisting proteinuria or chronic hypertension to 28 percent when one or both of these conditions were present (odds ratio [OR], 1.75 [95% CI, 1.02 to 3.01]).⁴⁵

Other risk factors based on medical history are also used for risk-stratified clinical preventive services. For example, the U.S. Preventive Services Task Force (USPSTF) recommends a pragmatic approach to identify patients at low, moderate, or high risk for preeclampsia in its recommendation on low-dose aspirin prophylaxis in pregnancy.⁴⁶ The National Institute for Health and Care Excellence (NICE) risk assessment approach is similar (**Table 2**).⁴⁷ High-risk pregnant women include those with a history of preeclampsia, multifetal gestation, chronic hypertension, type 1 or 2 diabetes, renal disease, or autoimmune disease.⁴⁶ Moderate-level risk factors include nulliparity, obesity, family history of preeclampsia, sociodemographic

characteristics such as African American race or low socioeconomic status, age, or personal history factors (including low birth weight, previous adverse pregnancy outcome, and a pregnancy interval of more than 10 years).⁴⁶ A pregnant woman with a previous uncomplicated, full-term delivery is at lower risk for preeclampsia.⁴⁶

Rationale and Strategies for Screening

Screening for preeclampsia occurs periodically throughout pregnancy for all women receiving prenatal care. The aim of screening is to identify and diagnose the condition early in its course, to allow closer monitoring and effective disease management. Blood pressure measurement and testing for proteinuria have long been routine primary care screening tools for preeclampsia, and are core components of the diagnostic criteria. The timing of prenatal care visits, and the inclusion of both of these tests at every visit on a routine or indicated basis, is variable and not well described in the United States.

The gestational age at the time of diagnosis has a strong relationship with maternal and neonatal outcomes. Once diagnosed, care can be managed according to protocols that have been found to reduce the likelihood of maternal and neonatal harm. Depending on the timing of disease occurrence and spacing of visits, preeclampsia occurring at or very near term may not be detected during prenatal screening visits, but are likely to be detected when women present for delivery. The detection of earlier-term preeclampsia, particularly cases that develop before 34 weeks' gestation, is particularly important given the risks to the mother and neonate if severe disease features emerge.

Disease Management and Treatment

Effective management and treatment of diagnosed preeclampsia can prevent complications and poor health outcomes. Identification of women with preeclampsia allows health care providers to reduce the risk of eclampsia and maternal cerebral, vascular, hepatic, and renal complications. These most commonly occur among women who develop severe features of preeclampsia but can unexpectedly develop even in cases without severe features.⁴⁸ The clinically proven approaches for management of preeclampsia to reduce the likelihood of poor maternal and perinatal health outcomes include delivery, intravenous administration of magnesium sulfate, and treatment of high blood pressure. Importantly, delivery is the only curative treatment for preeclampsia once the condition develops; depending on the gestational timing of diagnosis and the seriousness of the maternal and fetal condition, induction of labor can reduce the risk of major morbidity and mortality. For women who develop severe preeclampsia, intravenous administration of magnesium sulfate is effective for reducing the risk of eclamptic seizures.^{49,50} Pharmacological treatment of very high blood pressure is recommended to reduce the risk of stroke and cerebral vascular events. These treatments are supported by a broad range of medical and public health organizations, including the World Health Organization, ACOG, and NICE.^{1,47,51} While there is variability in the strength of scientific evidence underlying different aspects of treatment,⁵² there is broad consensus that diagnosis and treatment improve perinatal and maternal health outcomes.^{1,53,54} A detailed discussion of the trial evidence for these interventions is

provided in **Appendix A**. Recent developments in prognostic evaluation using the fullPIERS (Pre-eclampsia Integrated Estimate of RiSk) model and other markers also hold promise for improving disease management.^{55,56}

Once a diagnosis of preeclampsia is made, increased maternal and fetal surveillance begin, and often referral to specialty care, with recommended treatments undertaken as needed during the course of monitoring. The clinical evidence for some management practices is less established than for others, but treatment is clearly associated with better outcomes in the case of magnesium sulfate, as well as early delivery in defined circumstances. Preeclampsia is among the most preventable causes of maternal mortality. Analyses of causes of maternal mortality from preeclampsia suggest that substandard clinical care often contributes to poor outcomes.⁵⁷ Delayed responses to clinical warning signs and ineffective management have been found to be contributing factors in the majority of cases.^{31,58} Data based on medical charts from the United Kingdom suggests that fewer than half of women who developed eclampsia were diagnosed with both hypertension and proteinuria in the week preceding the event (38%), and that preeclampsia with atypical presentation comprises a greater proportion of eclampsia cases, owing in part to delays in diagnosis.^{50,59} Inaccuracies in proteinuria tests or record keeping, however, could also account for a portion of these findings.

Rationale and Strategies for Risk Assessment

Early identification of women who are most likely to develop preeclampsia is potentially important for at least two reasons. First, women at higher risk may benefit from heightened surveillance and timely interventions if severe features of the disease appear, to mitigate the risk of negative health consequences for the mother and fetus.⁸ Second, low-dose aspirin for women at high risk, when commenced after the first trimester of pregnancy, ideally before 16 weeks' gestation, reduces the incidence of preeclampsia and the likelihood of experiencing serious complications, such as preterm birth and IUGR.^{60,61} Risk assessment generally relies on factors that are known to be associated with preeclampsia.^{42,62} However, no recommendations currently specify the use of clinical risk prediction tools for estimating a patient's individual risk for developing preeclampsia. Reviews of serum markers and uterine artery Doppler testing as singular prediction tools do not support their use in routine clinical care to identify women at great risk for preeclampsia.^{1,63,64} Efforts to develop multivariable predictive models for identifying women who will develop preeclampsia and its adverse consequences are ongoing.^{65,66}

Current Risk Assessment and Screening Practice in the United States

In the United States, the number of prenatal care visits and the specific tests used for screening may vary across clinical settings and populations. Risk factor assessment via medical history taking is a routine part of prenatal care and is included in Medicaid standards of practice for prenatal care.⁶⁷ Data from the National Maternal and Infant Health survey found that 80 percent of pregnant women had a medical history taken and 98 percent had their weight and height measured in the first or second prenatal visit.⁶⁸ Routine blood pressure measurement at prenatal

visits is recommended by most prenatal care guidelines, including ACOG, and is considered best practice.⁶⁷ In one survey, 96 percent of women reported receiving a blood pressure measurement at their first or second prenatal visit.⁶⁸ According to national data on health care utilization from 2004 through 2006, pregnant women received an estimated 4.26 (95% CI, 3.35 to 5.16) urinalysis tests per pregnancy, but the number varied by patient race, insurance status, geographic location, and risk status.⁶⁹ A 2007 survey of residency programs found that urine dipstick tests at every prenatal care visit was taught to 94 percent of respondents.⁷⁰ None of the prevailing clinical guidelines provide specific recommendations for the optimal number or interval of screening tests for preeclampsia in routine care (**Table 1**). Descriptions of the timing of routine prenatal care visits for healthy patients vary but generally suggest eight to 14 visits, with greater frequency closer to term.^{71,72}

General recommendations to screen for proteinuria throughout pregnancy are offered, although the value of proteinuria as a predictor of disease has been questioned. A systematic review including 11 studies (n=4,388) found low predictive accuracy for adverse outcomes from screening for total proteinuria; sensitivity was 35 percent and specificity was 89 percent.⁷³ It has also been suggested that due to the lack of sensitivity and specificity, routine protein dipstick testing should be reconsidered.^{69,74} The gold standard 24-hour urine protein test is not a practical screening tool, and there is increasing interest in the potential of using spot urine tests to determine the protein:creatinine ratio for diagnosis and point-of-care screening.^{1,75}

Several organizations have guidelines to identify women at greatest risk of developing preeclampsia that are based on the clinical judgment of providers, guided by an evaluation of risk factors that can be identified during a routine medical history (**Table 2**). No guidelines recommend the use of a specific risk assessment instrument or tool.

Previous USPSTF Recommendation

In 1996, the USPSTF recommended screening for preeclampsia with office-based blood pressure measurement using sphygmomanometry for all pregnant women at the first prenatal visit and periodically throughout the remainder of the pregnancy (B recommendation).⁷⁴ The 1996 evidence report did not contain an analytic framework or Key Questions (KQs), and it was not conducted as a systematic review according to current USPSTF procedures.

Chapter 2. Methods

Scope and Purpose

This report will be used by the USPSTF to update its 1996 recommendation on screening for preeclampsia and was developed using standard USPSTF procedures.⁷⁶ Investigators in collaboration with the USPSTF and the Agency for Healthcare Research and Quality (AHRQ) created an analytic framework incorporating the KQs and outlining the patient populations, interventions, outcomes, and potential adverse effects for this review (**Figure 1**). The target population includes pregnant women, including adolescents. All KQs include studies of high- and low-risk populations unless otherwise specified.

We sought high-level evidence on the value of screening for preventing health outcomes compared with no screening (KQ 1) and comparing different approaches to screening (KQ 1a). We also reviewed multivariable tools for assessing the risk of preeclampsia that could be used to identify women for whom screening and clinical care could differ (KQ 3). Evidence on the performance of routine screening tests for detecting preeclampsia (KQ 4) and on harms of risk assessment (KQ 3) and screening (KQ 5) were also reviewed to balance any negative, inadvertent effects that clinical screening might incur.

KQs and Analytic Framework

An analytic framework (**Figure 1**) and five KQs (listed below) were developed in consultation with USPSTF members.

1. How effectively does screening for preeclampsia reduce maternal and perinatal morbidity and mortality?
 - a. Does effectiveness differ by screening protocol (e.g., tests used, timing of tests, rescreening intervals) or preeclampsia risk status?
2. What is the effectiveness of risk assessment in early pregnancy for identifying women at high risk for preeclampsia?
3. What are the harms of preeclampsia risk assessment?
4. How effectively do screening tests (e.g., blood pressure, proteinuria) identify women with preeclampsia?
 - a. How accurate are different screening tests for proteinuria?
 - b. How effective are different screening protocols (e.g., instruments, test procedures, timing of tests, rescreening intervals) for identifying women with preeclampsia?
 - c. How should women at high risk for preeclampsia be screened differently from women at low or average risk?
5. What are the harms of screening for preeclampsia and do they differ by risk status or screening protocol?

Data Sources and Searches

We conducted an initial search for existing systematic reviews published from 1995 to February 17, 2014, in MEDLINE, PubMed, the Database of Abstracts of Reviews of Effects, the Cochrane Database of Systematic Reviews, and the Centre for Reviews and Dissemination Health Technology Assessment. We also reviewed systematic reviews and reports published by AHRQ, *British Medical Journal* Clinical Evidence, the Institute of Medicine, Clinical Key, DynaMed, and NICE. The literature search strategies can be found in **Appendix B**.

We performed comprehensive literature searches for primary literature in the MEDLINE, PubMed, and Cochrane Central Register of Controlled Trials databases from 1990 through September 1, 2015 (**Appendix B**). We excluded studies published before 1990, as changes in diagnostic criteria and treatments made data from the preceding era less applicable to practices in the past 25 years. Before 1990, relative increases in blood pressure or mean arterial pressure and the presence of edema were included in the diagnostic criteria, so those screening approaches would not be applicable to current practices or the disease definition. Moreover, important developments in the prevention of eclampsia with magnesium sulfate and in the treatment of early-preterm babies with lung surfactants occurred in the late 1980s and early 1990s, changing the balance of harms and benefits with regard to health outcomes for different preeclampsia screening and management strategies. Nevertheless, we remained attentive to the possibility that a landmark study predating 1990 could be relevant to our review and therefore included references from the 1996 USPSTF report. We reviewed reference lists of relevant studies and reviews to identify additional potentially relevant studies that were not identified by our literature searches. Additional references were obtained from expert reviewers.

Study Selection

Two investigators independently reviewed titles and abstracts using an online screening platform, Abstrackr.⁷⁷ The same investigators reviewed full-text articles against prespecified inclusion and exclusion criteria (**Appendix B Table 1**).

The diagnostic criteria for preeclampsia have changed over time and vary worldwide (**Appendix C**).⁷⁸ Any standard diagnostic criterion for preeclampsia was allowed, as defined by the study. For evidence on KQs pertaining to the benefits and harms (KQs 1 and 5) of preeclampsia screening for maternal, fetal, and infant health outcomes and the accuracy of screening for detecting women with preeclampsia (KQ 4), we considered studies of screening occurring from 20 weeks' gestation until delivery, since widely used diagnostic criteria for preeclampsia specify that screening occur after 20 weeks' gestation.^{1,79} For KQs relating to risk assessment (KQs 2 and 3), we included studies evaluating risk assessment tools applied in the first 20 weeks of pregnancy, prior to the onset of disease as defined by the diagnostic criteria for preeclampsia. One purpose of risk assessment would be to identify high-risk patients who are eligible for low-dose aspirin prophylaxis, which may be more beneficial when begun early in the second trimester.^{80,81} Eligible study populations were pregnant women without a diagnosis of preeclampsia and asymptomatic for the condition. We did not exclude studies that included pregnant women with common chronic conditions often seen in primary care settings (i.e.,

chronic hypertension and diabetes mellitus) or those at elevated risk for preeclampsia. We did, however, exclude studies that solely focused on women seeking high-risk obstetric care, infertility treatment, inpatients, and other nongeneralizable populations with select preexisting health conditions.

Health outcomes considered for KQ 1 were any benefits or harms related to maternal, fetal, or infant health. We placed priority on health outcomes known to be directly related to preeclampsia, such as eclampsia, HELLP syndrome, organ damage or failure, fetal growth restriction, preterm delivery, low birth weight, stillbirth, and placental abruption, some of which are associated with both short- or long-term health and developmental consequences.

Screening and risk assessment interventions considered were point-of-care tests, measures, and evaluations conducted in routine primary prenatal care. For screening, point-of-care blood pressure measurements using manual or automated devices and point-of-care urine tests for proteinuria with qualitative, quantitative, visual, or automated readings were included. When assessing the diagnostic accuracy of point-of-care urine tests used to detect proteinuria (KQ 4a), we excluded studies that did not use a 24-hour urine test as the reference standard. Secondary evaluations and tests used to assess preeclampsia severity or to confirm diagnosis were not included.

For risk assessment (KQ 2), our a priori inclusion/exclusion criteria aimed to include externally validated multivariable risk assessment tools that used patient history and routinely collected clinical measures (e.g., BMI, weight, blood pressure). We subsequently broadened our inclusion/exclusion criteria for risk assessment tools based on the low yield of potentially eligible studies, since most externally validated models to date also include serum markers, Doppler measures, or both. The serum marker and Doppler reading could be available for women who opt for aneuploidy testing in the first or early second trimester of pregnancy. Approximately 67 to 72 percent of pregnant women in the United States participate in aneuploidy screening,⁸² so these markers could be available for a large proportion of prenatal care patients.

Our inclusion criteria specified that we would exclude models that were not externally validated (i.e., models not tested in another population than the derivation study, assessing either performance or impact); internal validation studies are suited best to the population in which they were derived, and most biases of internal validation studies are in the direction of overly optimistic results.^{83,84} Testing the predictive algorithm in a new population, ideally with a new study team, gives an approximation of the performance to be expected with broader application of a tool.

In the hierarchy of risk prediction tool validation, randomized impact studies are most valuable for purposes of clinical implementation since they give evidence on the expected effect of clinical application of the tool on health outcomes.⁸⁵ The ideal impact study design would compare standard care to care with the risk assessment tool in a randomized, controlled trial (RCT). The second-best level of evidence for a risk assessment tool comes from well-conducted external validation studies of a model in a different cohort (i.e., time, place, or both) by different investigators. External validation is important given that many of the threats to validity in model

development studies lead to overestimation of model performance (e.g., overfitting, selection of parameters).

We did not include studies not published in English or in which the majority of participants were from countries that are not designated as having a very high Human Development Index, as defined by the United Nations Development Programme (2014).⁸⁶ Studies conducted in other settings are less likely to offer evidence that would translate to the U.S. primary care setting in terms of the laboratory testing operations, screening modes, access and use of health care, treatments, and health outcomes. A list of excluded studies and reason for exclusion are provided in **Appendix D**.

Quality Assessment and Data Abstraction

Two investigators independently assessed the quality of all included studies using criteria predefined by the USPSTF⁸⁷ and supplemented them with other criteria from the Quality Assessment of Diagnostic Accuracy (QUADAS) II for diagnostic accuracy studies (KQ 4a),⁸⁸ the Newcastle-Ottawa Scale (NOS),⁸⁹ and the Before After Quality Assessment tool⁸⁹ for observational studies (KQs 3 and 5) (**Appendix B Table 2**). The critical appraisal of risk prediction models (KQ 2) was developed for this review based on recent guidance on reporting on and quality appraisal for multivariable risk prediction models.^{83,85} Each included study that was appraised with a quality rating tool received a final quality rating of good, fair, or poor, and disagreements in quality were resolved through discussion. We excluded poor-quality studies (i.e., attrition >40%, differential attrition >20%, or other fatal flaws or cumulative effects of multiple minor flaws or missing information significant enough to limit our confidence in the validity of results). Good-quality studies met all or most of the assessment criteria. We rated studies as fair if they did not meet most of the good quality criteria.

One investigator abstracted data from all included studies into a Microsoft Access® database (Microsoft Corporation, Redmond, WA). A second investigator checked the data for accuracy. We abstracted study design characteristics, baseline population demographics, screening and risk assessment characteristics, health outcomes, adverse events, and diagnostic accuracy where applicable.

Approach to Review of Clinical Risk Prediction Studies

Our approach to the appraisal of the external prediction models identified in our literature search was informed by recent guidance articulated in the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) Statement⁸⁵ and the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies (CHARMS).⁸³ We used domains defined in both the TRIPOD statement and CHARMS tool, as well as related methods reports,^{83-85,90,91} to evaluate the externally validated risk prediction tools we identified. No published tool for quality appraisal of external model validation studies is currently available; existing guidance is focused on risk of bias in model development and internal validation studies. Since we included only models that have been subjected to external validation, the bias risks outlined in CHARMS regarding problems with

overfitting and overoptimistic performance were not as relevant, since these are generally addressed through the process of external validation. Therefore, we did not exclude any of the modeling studies for quality concerns and instead described the performance of all of the externally validated models we identified, providing detailed information on the validation studies and reported measures of model performance. More details on methodological considerations that informed our evaluation of risk prediction models are available in **Appendix E**.

Measures of Risk Prediction Model Performance

Discrimination was consistently reported using the concordance index (c-statistic), or area under a receiver operator curve plot, which represents the probability that a case will have a higher risk score than a non-case will. The degree to which a model correctly orders true positive and true negative results is represented by this statistic. Discrimination is also described with sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). A priori risk-level cutpoints are optimal, but in this literature, “detection rates,” analogous to sensitivity, were commonly reported with risk cutpoints corresponding to a 10 percent false-positive rate (90% specificity).⁸³

Calibration is another measure of model performance that reflects the extent to which the model predictions match the observed outcomes for individuals across risk levels. Goodness-of-fit tests (e.g., Hosmer-Lemeshow test) are sometimes used to report calibration, but calibration plots that graphically depict the observed outcome frequencies against predicted probabilities are more informative.⁸⁵ Principles that are the basis for the TRIPOD statement indicate that discrimination and calibration are both “fundamental” for evaluating model performance in validation studies.⁸⁵

Data Synthesis and Analysis

We created summary evidence tables for each of the KQs that include important population characteristics and study design features.

Our analysis was primarily qualitative owing to the low number of included studies identified for each KQ. For KQ 2, we focused our reporting on models having at least good discrimination but extracted data from all models. In evaluating c-statistic values we defined values below 0.70 as inadequate, from 0.70 to 0.79 as adequate, and 0.80 or higher as good to excellent.⁹² Our description of externally validated models focused on those with good to excellent discrimination.

Quantitative meta-analysis was conducted only for KQ 4a. We calculated the diagnostic accuracy of point-of-care urine tests using the 24-hour urine collection as the reference standard (significant proteinuria defined as 300 mg with exertion over the 24-hour collection). We converted all urine excretion ratios to mg/mmol by converting any values to mg/g and multiplying this value by 0.113.⁷⁵ We stratified results by the type of point-of-care index test: protein:creatinine, albumin:creatinine, and protein dipstick. For studies reporting multiple thresholds, we selected the most clinically acceptable cutoff for each urine test to be used when

pooling (30 mg/mmol,⁹³ 2.0 mg/mmol,⁹⁴ and 1+, respectively). Due to the small number of studies evaluating the diagnostic accuracy of the albumin:creatinine tests and protein dipstick, we qualitatively described the results and visually displayed the data. For studies evaluating the diagnostic accuracy of protein:creatinine tests, we ran bivariate analyses to simultaneously examine sensitivity and specificity using the “midas” meta-analysis for diagnostic accuracy command in Stata version 13.1 (Stata Corp LP, College Station, TX). The pooled sensitivity and specificity, heterogeneity, and pooled receiver operator curve (ROC) were calculated when enough studies using the same index test and reference standard were identified (≥ 8 studies). Our strategy for exploring heterogeneity was to examine patterns in the results based on population, intervention, comparator, outcomes, timing, and setting factors that might be associated with different findings. Factors we expected to be important a priori included the index test threshold, clinical setting, and inclusion criteria. For example, we stratified women by the entry criteria of enrollment due to high blood pressure, enrollment due to high blood pressure or other indications for proteinuria screening, and previous positive (+1) urine protein dipstick result. We conducted random-effects meta-regression using the “metareg” procedure in Stata to statistically test the contribution of factors likely to explain heterogeneity based on the patterns observed in the stratified test accuracy results. We used the restricted maximum likelihood method with the Knapp-Hartung adjustment.⁹⁵

We conducted sensitivity analyses, excluding studies that did not provide complete 2×2 results (e.g., studies reporting sensitivity and specificity only), those with cutoffs beyond 30 ± 5 mg/mmol, and those that were not at a threshold of 30 mg/mmol.⁹⁶

Statistical meta-analysis was not performed for all outcomes because of methodological limitations of the studies and heterogeneity in study designs, interventions, populations, and other factors, but we did conduct them when appropriate. Studies included in prior reviews were reviewed for consistency with current results; however, lack of studies and differences in scope, KQs, and inclusion criteria limited aggregate synthesis with the updated evidence.

Expert Review and Public Comment

A draft research plan for this review was available for public comment from May 22 to June 18, 2014. The draft version of this report was reviewed by content experts, USPSTF members, AHRQ Medical Officers, and federal partners.

USPSTF Involvement

This research was funded by AHRQ under a contract to support the USPSTF. We consulted with four USPSTF liaisons during the development of the research plan. An AHRQ Medical Officer provided project oversight and reviewed the draft report. The USPSTF and AHRQ had no role in the study selection, quality assessment, or writing of the systematic review.

Chapter 3. Results

Literature Search Results

We screened 10,082 abstracts and 378 full-text articles to identify 21 included studies reported in 35 publications (**Appendix B Figure 1**).^{94,97-130} We did not identify any studies that directly compared the effectiveness of preeclampsia screening in a screened population versus an unscreened population (KQ 1). We included one RCT⁹⁷ on the benefits and harms of differing visit schedules for preeclampsia screening for both KQs 1a and 5 and one observational before-after study that assessed potential harms of different screening strategies (KQ 5).¹¹⁵ We identified four studies reporting on the external validation of preeclampsia risk prediction models (KQ 2)⁹⁸⁻¹⁰¹ and a single observational study evaluating the harms of risk assessment (KQ 3).¹⁰² We did not identify any studies evaluating the effectiveness of screening tests for identifying women with preeclampsia (KQ 4). We included 14 studies examining the diagnostic accuracy of urine tests for proteinuria (KQ 4a), which included comparisons of the test accuracy of different approaches to urine protein screening (KQ 4b).^{94,103-114,119}

Results of Included Studies

KQ 1. How Effectively Does Screening for Preeclampsia Reduce Maternal and Perinatal Morbidity and Mortality?

No studies directly compared the effectiveness of preeclampsia screening in a screened population versus an unscreened population.

KQ 1a. Does Effectiveness Differ by Screening Protocol or Preeclampsia Risk Status?

Summary

One RCT conducted among 2,764 “low-risk” insured women seeking prenatal care in the first trimester in the early 1990s found that five fewer scheduled prenatal care visits (and thus fewer preeclampsia screenings) did not result in worse birth outcomes. However, the difference in the number of visits between groups was smaller than intended and the power to detect differences was insufficient for some important health outcomes.

Evidence

One fair-quality RCT randomized 2,764 pregnant women, enrolled from 1992 to 1994, ages 18 to 39 years presenting for their intake visit in the first trimester to a routine number of prenatal care visits (14 visits) or a schedule of fewer visits (nine visits) (**Appendix F Tables 1–3**).⁹⁷ A total of 2,328 women completed the study: 1,163 in the control group and 1,165 in the intervention group. The study sought to enroll “low-risk” women; the most common reasons for

exclusion were: presenting too late for the first prenatal care visit (17% of women making their first visit arrived after 13 weeks' gestation), being outside the included age range, and having a previous high-risk obstetric condition or a medical condition. Past high-risk conditions included preterm delivery, preterm labor, abruption, severe preeclampsia, cesarean delivery (vertical incision), gestational diabetes, incompetent cervix, uterine anomaly, diethylstilbestrol exposure, isoimmunization, more than one second-trimester abortion, fetal anomaly, or SGA neonate. Current high-risk medical conditions included diabetes, chronic hypertension, drug or alcohol abuse, multiple gestation, conception through assisted reproductive technology, and large (≥ 4 cm) leiomyomata.

Routine prenatal care consisted of visits every 4 weeks between 8 and 28 weeks' gestation, then every 2 weeks until 36 weeks' gestation, then weekly until delivery, for a total of 14 prenatal care visits. For the intervention, the number of visits was reduced to nine; they occurred at 8, 12, 16, 24, 28, 32, 36, 38, and 40 weeks' gestation. In both groups, the initial visit consisted of routine blood analysis, Papanicolaou test, and gonorrhea and chlamydia screening; later tests included serum alpha-fetoprotein screening (15 to 18 weeks' gestation), gestational diabetes screening with the 1-hour glucose tolerance test and hematocrit (24 to 28 weeks' gestation), and antibody screening (28 weeks' gestation). Ongoing risk assessment occurred at each visit, which included blood pressure screening and urine testing for glucose and protein.

At baseline, there were no statistically significant differences between groups in maternal characteristics. During pregnancy, women in the control group had more health care visits in total ($p < 0.001$), with a provider ($p < 0.001$), and with a nurse ($p = 0.04$) than did women in the intervention group, although the mean difference in the number of visits between the two study groups was smaller than intended (12.0 ± 4.2 vs. 14.7 ± 4.2 ; $p < 0.001$). At the time of delivery, there were no statistically significant differences between groups in maternal outcomes (e.g., gestational diabetes, preeclampsia), delivery complications (e.g., preterm delivery, cesarean delivery, postpartum hemorrhage), or neonatal outcomes (e.g., birth weight, gestational age, stillbirth) (**Table 3**). At 6 weeks postpartum, there were also no statistically significant differences between groups in satisfaction with prenatal care. More women in the intervention group than the control group felt the number of prenatal care visits was "just right" ($p = 0.002$). Overall, reducing the number of prenatal care visits did not clearly affect health outcomes.

KQ 2. What Is the Effectiveness of Risk Assessment in Early Pregnancy for Identifying Women at High Risk for Preeclampsia?

Summary

We identified five multivariable risk prediction models whose external validation studies ($k=4$) indicated, based on the c-statistic, good or better discrimination. Three of the models (Models A, B, and C) aimed to predict early-onset preeclampsia (requiring delivery) and two to predict preeclampsia occurring or requiring delivery after 34 weeks (Models D and E). The models predicting early-onset preeclampsia included clinical indicators, serum markers, and the uterine artery pulsatility index as parameters on which risk prediction was based, whereas models for predicting later preeclampsia did not include serum markers. Detection (i.e., sensitivity of the risk-based prediction model at a 90% specificity cutpoint) was generally low (52% to 92%) with

wide CIs, and PPV was low (4% to 39%) for all of the models. The relationship between the predicted probabilities and observed outcomes (calibration) was not reported, so we could not evaluate model performance with this important metric. There was no clear evidence of high performance or clinical benefits for any of the externally validated models.

Evidence

Seven articles reported on results for four external validation studies (for 16 models) (**Table 4; Appendix B Figure 1; Appendix G**).^{98-101,116-118} Six models were developed for prediction of preeclampsia requiring delivery before 34 weeks' gestation,^{121,122,124,127,128,130} one before 37 weeks' gestation,¹²⁰ seven after 34 weeks' gestation,^{123-127,129,130} and two at any time.^{120,126} External validation of the five models in the Italian cohort⁹⁸ was for prediction of preeclampsia diagnosed after 34 weeks' gestation, regardless of delivery status. An additional 11 articles reported on the model development studies related to these external validations.¹²⁰⁻¹³⁰ Each external validation study⁹⁸⁻¹⁰¹ had at least one model with a c-statistic indicating discrimination of 0.80 or higher, with a total of five models meeting this standard (**Table 5**).^{120,122,123,127} Models were labeled A through E for clarity of communication.

The external validation of models A through E was conducted using prospective cohort data collected in the United States by Oliveira et al (n=2,962),⁹⁹ in Australia by Park et al (n=3,014),¹⁰⁰ in Italy by Farina et al (n=554),⁹⁸ and in Norway by Skrastad et al (n=541).¹⁰¹ The Farina and Park studies enrolled women with singleton pregnancies presenting for aneuploidy screening, the Oliveira study enrolled women with singleton pregnancies presenting for prenatal care in the first trimester, and the Skrastad study enrolled nulliparous women. All of the cohorts were enrolled sometime between 2007 and 2012.

The external validation study evaluating the performance of Models A and B within a U.S. cohort of women with singleton pregnancies presenting in the first trimester for prenatal care at one of four centers in Baltimore, MD, was identified as the most likely to provide results applicable to U.S. prenatal care patients.⁹⁹ Of these two models, Model B had better discrimination and detection and had also been developed in a U.S. population by Odibo et al.¹²² Model B used clinical history, placental protein 13, pregnancy-associated plasma protein A, and the mean artery pulsatility index (c-statistic, 0.86) to predict preeclampsia-required delivery before 34 weeks' gestation. It was validated with a smaller subset of the available cohort (n=871; 29% of the 2,969 women in the external validation cohort) because not all women had data on one of the serum markers needed for the model. Model B was initially developed and internally validated in a cohort of women presenting for aneuploidy screening, where discrimination and detection were similar to the external validation results.¹²²

Model A was the only risk tool externally validated in more than one setting.^{99,100} In the U.S. cohort validation study, discrimination was moderate (c-statistic, 0.80 [95% CI, 0.71 to 0.89]) and the detection (52%) and PPV (4.2%) were low based on 29 cases (1% incidence). The same model was externally validated in the Australian cohort of women with singleton pregnancies attending aneuploidy screening (n=3,014), where only 12 cases of early-onset preeclampsia occurred.¹⁰⁰ In that cohort, discrimination was high (c-statistic, 0.93 [95% CI, 0.92 to 0.94]), as was the detection (91.7% [95% CI, 61.5 to 98.6]), but the PPV was low (3.6%). Model A was

also evaluated in an observational study occurring alongside the Australian external validation cohort study to assess the impact of using the model to assign women to low-dose aspirin prophylaxis.¹¹⁸

High discrimination was seen for Model C when validated in a small Norwegian cohort of nulliparous women.¹⁰¹ The model was used to predict any preeclampsia requiring delivery before 37 weeks' gestation (c-statistic, 0.94 [95% CI, 0.86 to 1.00]). There were five cases of early-onset preeclampsia requiring delivery (0.9% incidence). Detection was 80 percent and the PPV was 6.8 percent. Models D and E used clinical history and uterine Doppler measures to detect later-onset preeclampsia; when validated with a small Italian cohort, they had good to excellent discrimination, with detection of 85 and 74 percent and PPVs of 39.3 and 36.3 percent, respectively.^{123,127}

Information on model calibration was not provided in any of the model external validation studies, precluding a complete assessment of model performance. There were no randomized impact studies evaluating the effects of these models when used as risk assessment tools in clinical application relative to usual care.

KQ 3. What Are the Harms of Preeclampsia Risk Assessment?

Summary

One fair-quality prospective cohort study (n=255) found no differences in anxiety before and after counseling on preeclampsia risk and categorization as high or low risk based on results of a multivariable risk prediction model. High-risk women were subject to changes in their clinical care, with usual care for the low-risk group. Measures of anxiety over time did not change but were collected from less than half of the study participants.

Evidence

We identified one fair-quality, prospective cohort study conducted in Spain that examined whether first-trimester risk assessment and clinical care protocols based on risk status increased anxiety in pregnant women (**Appendix F Tables 1–3**).¹⁰² Risk for early-onset preeclampsia requiring delivery before 34 weeks was assessed using a model developed in Spain¹³⁰ and externally validated in a U.S. cohort⁹⁹ (**Appendix G**). Pregnant women screened as high risk were recruited and matched with the next low-risk screened woman in the first trimester screening unit (n=255; 135 low-risk, 120 high-risk).

After risk assessment, all participating women were provided counseling on the potential risks of preeclampsia. Women at high risk underwent a followup management protocol that included recommended daily intake of acetylsalicylic acid (150 mg) from the day of screening until 36 weeks' gestation and second-trimester ultrasonography at 20 to 22 weeks that included uterine artery Doppler velocimetry.¹⁰² There were no statistically significant differences in the demographic characteristics of women screened as high versus low risk at the enrollment visit.¹⁰²

Anxiety levels were assessed within 1 hour post-counseling using a self-reported anxiety

questionnaire (Spielberg State-Trait Anxiety Inventory [STAI]) to measure trait (STAI-T) and state (STAI-S) anxiety.¹⁰² Study participants completed the STAI-T on the day of preeclampsia screening (prior to risk counseling) and were asked to answer the STAI-S immediately after the counseling visit. In a subgroup of women (51 low-risk and 50 high-risk), anxiety levels were also measured during the second and third trimesters (data not shown).

At baseline, low- and high-risk women did not differ in STAI-T scores (41.2 [standard deviation (SD), 6.7] vs. 40.4 [SD, 8.1]; $p=0.35$).¹⁰² After risk assessment and counseling, STAI-S scores for low- and high-risk women were 35.0 (SD, 9.9) and 34.6 (SD, 10.1), respectively ($p=0.77$).¹⁰² The proportion of women with high anxiety was also not significantly different between the two groups (28/134 [20.7%] vs. 24/120 [20%]; $p=0.88$). Measurements of anxiety levels taken during the second and third trimesters indicated no differences in the low- and high-risk subgroups, but less than half of the baseline participants provided data for these comparisons (data not shown).¹⁰² Overall, first-trimester preeclampsia risk assessment and counseling did not increase maternal anxiety, but risk assessment was coupled with counseling for all women and changes in clinical care for high-risk patients.

KQ 4. How Effectively Do Routine Screening Tests Identify Women With Preeclampsia?

We found no evidence to evaluate the effectiveness of routine screening tests in identifying women with preeclampsia. Such studies would have evaluated how accurately clinical blood pressure measurement or urinalysis identified women with the diagnosis of preeclampsia at that time. The only available evidence was for various screening approaches for establishing the presence of proteinuria (one diagnostic criterion for preeclampsia).

KQ 4a. How Accurate Are Different Point-of-Care Screening Tests for Proteinuria?

Summary

Fourteen studies evaluated the diagnostic accuracy of urine tests in detecting proteinuria compared with 24-hour urine collection (reference standard). All of the studies examined the test performance of protein urine testing in women with suspected preeclampsia. None considered accuracy in the context of repeated testing. The limited and variable evidence on test accuracy did not support conclusions about which test would perform best for routine screening. Twelve studies evaluated protein:creatinine test sensitivity (range, 0.65 to 0.96; $I^2=80.5%$; 11 studies) and specificity (range, 0.49 to 1.00; $I^2=91.8%$; 11 studies). Studies conducted among women with 1+ or higher dipstick protein at enrollment had higher test sensitivity than those conducted among women seen for other indications of suspected preeclampsia (e.g., de novo hypertension). Two studies evaluating albumin:creatinine urine tests had similarly high sensitivity (0.94 and 1.00) and disparate specificity (0.94 and 0.68). Four studies tested the accuracy of automated protein dipstick test ($\geq 1+$), with variable results—only one protein dipstick test had evidence of both specificity and sensitivity greater than 80 percent. Spectrum bias likely influenced all of the study results, so these are probably overestimates of the likely test performance in routine

prenatal care.

Evidence

We identified 14 studies (four good-quality and 10 fair-quality) evaluating the accuracy of different screening tests for proteinuria (**Appendix F Tables 1 and 2**).^{94,103-114,119} Twelve studies evaluated protein:creatinine urine tests,^{103-111,113,114,119} two studies evaluated albumin:creatinine urine tests,^{94,106} and four studies evaluated urine protein dipstick tests (**Figure 2; Table 6**).^{94,105,106,112} Most studies evaluated the test performance characteristics for significant proteinuria across a wide range of thresholds (**Appendix F Table 4**). The reference standard for inclusion was 24-hour urine collection; all studies used a urinary protein excretion threshold of 300 mg over 24 hours to diagnose significant proteinuria. The prevalence of significant proteinuria ranged from 8.7 to 93.8 percent (**Appendix F Table 3**). Four studies evaluated test performance characteristics for identifying severe proteinuria (e.g., urinary protein excretion threshold of $\geq 3,000$ mg over 24 hours); all urine tests performed as well as expected and are not further discussed (**Appendix F Table 5**).^{104,105,113,119}

All studies were conducted in pregnant women with suspected preeclampsia, which included those referred to 24-hour urine collection for suspected preeclampsia, chronic or de novo hypertension, and/or proteinuria (i.e., tested positive on at least one previous protein dipstick). Study participants were generally in their late 20s and early 30s and were evaluated near the end of their third trimester of pregnancy. The majority of studies were conducted in predominantly white populations; other racial/ethnic groups were underrepresented. Personal or family history of preeclampsia was not reported. Six studies were conducted in the United States,^{104,105,109,110,113,114} four in the United Kingdom,^{94,103,108,112} one in New Zealand,¹⁰⁶ one in Canada,¹⁰⁷ one in Chile,¹¹⁹ and one in the Netherlands.¹¹¹

Twelve studies evaluated the accuracy of protein:creatinine urine tests in 1,516 pregnant women (**Figure 2**).^{103-111,113,114,119} One study did not provide the raw data necessary for pooled analyses and we were unable to retrieve the data from the study authors, but the reported sensitivity and specificity are included in our results narrative.¹¹⁴ Only one study reported the make or manufacturer of the protein:creatinine urine test being evaluated (Albustix, Siemens Healthcare Diagnostics, Malvern, PA).¹¹¹ Sensitivity of the protein:creatinine urine test ranged from 0.65 (95% CI not calculable)¹¹⁴ to 0.96 (95% CI, 0.88 to 0.99),¹¹¹ with most studies reporting sensitivity greater than 0.81; the combined sensitivity (k=11) was 0.85 (95% CI, 0.78 to 0.90), with high heterogeneity ($I^2=80.5\%$) (**Appendix F Figure 1**). Specificity ranged from 0.49 (95% CI, 0.36 to 0.63)¹¹⁰ to 1.00 (95% CI, 0.16 to 1.00);¹⁰⁸ the combined specificity (k=11) was 0.85 (95% CI, 0.72 to 0.92), with very high heterogeneity ($I^2=91.8\%$). In pooled ROC analysis (**Appendix F Figure 2**), the area under the curve (AUC) was 0.91 (95% CI, 0.88 to 0.93), with similar numbers of studies in the space above the curve and below. The dispersion of study data points reflects the considerable heterogeneity seen for both sensitivity and specificity and limits drawing summary conclusions about overall performance from the pooled ROC analysis.

To evaluate statistical and clinical heterogeneity, we examined the data using forest plots sorted by theoretically plausible factors. A correlation between test accuracy and the degree of likely spectrum bias was observed. Studies enrolling patients with a 1+ or higher dipstick

result^{103,108,111} or including any patients already diagnosed with preeclampsia¹¹⁰ would likely be subject to greater spectrum bias than those recruiting all patients with 24-hour tests for suspected preeclampsia, regardless of indication.^{105,107,109,119} Three studies fell somewhere in the middle, where patients could be enrolled with a 1+ or higher protein dipstick reading but also for other specific indications (e.g., worsening hypertension) that did not require a positive protein dipstick result.^{104,106,113} Sorting by the population enrolled, we observed that most of the highest sensitivities were in studies that enrolled only patients with a positive dipstick test; differences between groups were statistically significant in meta-regression (**Appendix F Figure 3**). Heterogeneity was low after adjustment for enrollment criteria ($I^2=15.9\%$). For specificity, however, these differences did not explain the high statistical heterogeneity, nor were alternative explanations found. Poor reporting across the included studies on the specific type of test assay limited our ability to evaluate the possible contribution of the index test used against the observed heterogeneity.

Two studies evaluated the accuracy of albumin:creatinine urine tests in 321 pregnant women.^{94,106} Both studies evaluated the DCA 2000 point-of-care system (Bayer Healthcare, Whippany, NJ) that estimates albumin:creatinine in 7 minutes from a 40- μ L urine sample utilizing immunoturbidometric (albumin) and colorimetric (creatinine) assays. The samples were collected before the 24-hour urine collection was initiated⁹⁴ or in the early morning before the final 24-hour specimen.¹⁰⁶ Sensitivity was similar at the common threshold of 2.0 mg/mmol, but specificity differed (**Figure 2**). Sensitivity was 0.94 (95% CI, 0.85 to 0.98) and specificity was 0.94 (95% CI, 0.87 to 0.98) in the good-quality study of 171 pregnant women (45% significant proteinuria).⁹⁴ In the fair-quality study of 150 pregnant women (8.7% significant proteinuria), sensitivity was 1.00 (95% CI, 0.75 to 1.00) and specificity was 0.68 (95% CI, 0.59 to 0.76).¹⁰⁶ This study also evaluated the albumin:creatinine urine test at two other thresholds (3.5 and 8.0 mg/mmol) and found similar sensitivity (1.00) and higher specificity than for studies using the 2.0 mg/mmol threshold (0.88 and 0.96, respectively) (**Appendix F Table 4**).

The good-quality study in 171 pregnant women also evaluated the Microalbustix and Clinitek albumin:creatinine urine dipsticks (Bayer Healthcare, Whippany, NJ).⁹⁴ The Microalbustix dipstick was read visually by two observers, while the Clinitek dipstick could only be read on the Clinitek 50 urine chemistry analyzer. The visually read Microalbustix dipstick had lower sensitivity (0.49 [95% CI, 0.38 to 0.61]) than the automated Clinitek dipstick (0.58 [95% CI, 0.47 to 0.70]) but identical specificity (0.83 [95% CI, 0.74 to 0.90]) (**Appendix F Table 4**).

Four studies evaluated the accuracy of protein dipsticks in 634 pregnant women with mixed test performance characteristics.^{94,105,106,112} None of the protein dipsticks were the same make or model; only the reference standard (benzethonium chloride [BEC] assay) was similar between studies. Two studies obtained the urinalysis sample before the initiation of the 24-hour collection,^{105,106} the other two studies used aliquots from the thoroughly mixed 24-hour collection.^{94,112} Sensitivity ranged from 0.22 to 1.00 and specificity ranged from 0.36 to 1.00 (**Figure 2**). Of these, only one study had both sensitivity and specificity greater than 0.80.⁹⁴ This good-quality study of 171 pregnant women evaluated visual reading by two observers and automated reading using the Clinitek 50 urine chemistry analyzer of the Multistix 8 SG dipstick (Bayer Healthcare, Whippany, NJ).⁹⁴ The visually read protein dipstick had a lower sensitivity (0.51 [95% CI, 0.39 to 0.62]) than the automated reading (0.82 [95% CI, 0.71 to 0.90]) but

specificity was similar (0.78 and 0.81, respectively). Apart from that study, the others had very high sensitivity and low specificity or vice versa (**Appendix F Table 4**).

KQ 4b. How Effective Are Different Screening Protocols for Identifying Women With Preeclampsia?

Summary

There was no evidence evaluating the effectiveness of blood pressure or urine screening for identifying women with preeclampsia and no evidence to inform comparisons among various screening protocols using these tests. However, a few of the studies for KQ 4a on various screening approaches for detecting proteinuria, a diagnostic criterion for preeclampsia, reported on the effect of variations in urine sample collection, assay methods, and reading approaches for urine screening tests. On the basis of the included studies for KQ 4a, within-study comparisons suggest that automated rather than visually read tests have higher test performance, the time of day of testing is not predictive of performance for the protein:creatinine test, and the sensitivity of tests depends on the 24-hour test assay used.

Evidence

Visual Versus Automated Readings

One good-quality study compared visual and automated readings of protein dipsticks and albumin:creatinine urine tests in 171 pregnant women.⁹⁴ Two trained observers, who were blinded to each other's readings, visually read the results of the tests and the same samples were then retested using the automated analyzers. For both types of tests, the visual reading had lower performance than the automated reading (**Appendix F Table 4**).

Time of Urine Sample Collection

One good-quality study evaluated the test performance characteristics of the Albustix protein:creatinine urine test when collected from 105 pregnant women in the morning (8:00 a.m.), afternoon (12:00 p.m.), and evening (5:00 p.m.).¹¹¹ Using a protein:creatinine excretion threshold of 30 mg/mmol, there were no statistically significant differences in the sensitivity ($p=0.12$) and specificity ($p=0.89$) between timepoints (**Appendix F Table 4**).

24-Hour Assay

One fair-quality study evaluated the test performance characteristics of the BM-Test 5L urine protein dipstick (Boehringer Mannheim, East Sussex, UK) and compared it with two standard qualitative protein assays using the pooled 24-hour urine collection (BEC assay and the Bradford assay) in 197 pregnant women with hypertension.¹¹² The BEC assay is an immunoturbidometric assay that is the most frequently used method in clinical practice to assess proteinuria in a 24-hour collection aliquot.¹³¹ The Bradford assay is based on the ability of proteins in the urine to bind to Coomassie blue dye and is more frequently used in laboratories.¹³² The prevalence of significant proteinuria among 197 women varied greatly between assays (70.1% for BEC assay

and 24.9% for Bradford assay); therefore, the sensitivity of the dipstick was markedly different between assays (0.22 vs. 0.57, respectively), while the specificity was similar (0.98 and 0.97, respectively) (**Appendix F Table 4**).

KQ 4c. How Should Women at High Risk for Preeclampsia Be Screened Differently From Women at Low or Average Risk?

We found no evidence that compared different screening strategies among women at high risk for preeclampsia versus women at low or average risk.

KQ 5. What Are the Harms of Preeclampsia Screening and Do They Differ by Risk Status or Screening Protocol?

Summary

Two fair-quality studies were identified that reported on potential harms of different approaches to preeclampsia screening. Neither found evidence of harms, but both were underpowered to provide evidence on rare but important clinical outcomes.

Evidence

The fair-quality trial included for KQ 1a found no difference in birth outcomes (e.g., low birth weight, preterm birth, number of cesarean deliveries) with an intended reduction in the number of prenatal care visits from 14 to nine visits (**Table 3**).⁹⁷ The difference in the mean number of visits was not as great as expected (12.0 visits in the intervention group and 14.7 in the control group; $p < 0.001$). As previously noted, power was not sufficient to detect differences for rare outcomes related to preeclampsia, particularly serious adverse maternal events such as progression to eclampsia, organ failure, stroke, and death.

We also identified one fair-quality retrospective before-after comparison cohort study ($N=1,952$) that evaluated the differences in health outcomes after a change in the standard of care at a hospital-based nurse midwifery practice that primarily served low-income Hispanic women (74% of eligible study participants) from routine prenatal dipstick urine testing to “clinically indicated” urine testing (**Appendix F Tables 1–3**).¹¹⁵ All women in the study received urine tests at their first prenatal visit, but women giving birth before August 15, 2002 ($n=933$) received routine urine screening with chemical reagent strips testing for bacteria or protein at all subsequent visits, whereas women giving birth after August 15, 2002 ($n=1,019$) had subsequent urine screening only when certain conditions were indicated (symptoms of a urinary tract infection; severe vomiting; weight loss ≥ 0.9 kg since previous visit; SBP ≥ 140 mm Hg; DBP ≥ 90 mm Hg; or a condition requiring periodic urine testing, such as chronic hypertension or renal disease). Women who were enrolled before but gave birth after August 15, 2002 were excluded ($n=570$). The two cohorts delivering before and after the practice change were similar in terms of baseline characteristics except for insurance payment source ($p < 0.0001$).

Women in the routine urine testing group had used an average of 7.8 (range, 0 to 19) chemical

reagent strips—equivalent to the number of tests—while women in the indicated testing group had used an average of 1.4 (range, 0 to 16). Among the indicated testing group, the reasons for urine testing were urinary tract infection or vaginitis symptoms (31.5%) and elevated blood pressure or significant preeclampsia-related symptomatology (35.6%).

Since the purpose of the study was to evaluate whether changes in the urine screening approach were safe (i.e., did not change preeclampsia or other adverse condition diagnosis rates or other health outcomes), statistical tests were designed to evaluate noninferiority; thus, statistically significant p-values indicated equivalent diagnosis rates between the two groups (**Table 3**). These results suggest there were no differences in diagnosis rates of preeclampsia/eclampsia, high blood pressure, or gestational hypertension or in number of cesarean deliveries. Preterm delivery rates were not equivalent ($p=0.14$) but were lower with indicated testing (7.7% with routine testing vs. 4.9% with indicated testing). Overall, there was no evidence of reduced diagnosis of preeclampsia or adverse health outcomes when changing from routine to clinically indicated urine testing. There was also no evidence suggesting underdiagnosis of adverse outcomes related to urinalysis for bacteriuria.

Chapter 4. Discussion

Summary of Evidence

We reviewed externally validated multivariable models for predicting preeclampsia, most focusing on the prediction of early-onset disease, but did not identify a model with supporting evidence indicating readiness for clinical use. A few models had good discrimination (c-statistic ≥ 0.80), but CIs on estimates were wide, PPVs were low, and calibration statistics or plots were not provided, so it is not possible to determine likely performance in clinical use. As others have emphasized,^{85,133} at minimum predictive models must be externally validated and shown to have acceptable discrimination and calibration before they might be ready for clinical practice. Beyond that, it is desirable to determine the likely performance or clinical impact of these models.^{134,135} These evidence standards were not achieved by the currently available studies of predictive models in preeclampsia. Further, the serum markers and Doppler ultrasound tests used in the models require resource-intensive collection and evaluation using complex algorithms. Efforts are under way to externally validate models using more easily collected clinical history information.^{136,137}

Although we found considerable evidence on the accuracy of protein urine screening at a single time point in pregnancy, the studies were conducted in only women with suspected preeclampsia and thus are not representative of women presenting for routine prenatal visits. Of the different protein urine tests that can be conducted with point-of-care urine samples, protein dipstick tests are easy and low cost, but we identified only four eligible studies, which had highly variable results. The accuracy of albumin:creatinine tests was high, but only two studies contributed evidence. The majority of the evidence on accuracy was for protein:creatinine ratio tests, which can be conducted using a variety of tools (e.g., automated dipstick or aliquot readers, laboratory assays), but high heterogeneity precluded summary generalizations about performance. While these tests are often evaluated as a potential alternative to 24-hour urine collection for diagnostic confirmation, they have also been proposed for use in routine screening, particularly to rule out proteinuria.⁷⁵ The available evidence, however, does not facilitate conclusions about which point-of-care proteinuria test would be optimal for this purpose. There was considerable variation among tests, and the variation is difficult to explain given limitations in the evidence. Based on our findings and likely spectrum bias, we would expect quite variable and generally lower test accuracy performance in routine care of general prenatal care populations. Finally, no studies evaluated the performance of urine protein screening in the context of repeated testing, where false-negative results might be corrected over time.

Preeclampsia Screening for Reducing Morbidity and Mortality

We found no evidence that directly compared health outcomes in a screened population compared with an unscreened population (**Table 7**). One large trial, conducted in 1996 in a large health maintenance organization, suggested a schedule of somewhat fewer prenatal risk assessment and screening visits (and thus blood pressure and urine screening tests), which resulted in similar maternal and infant health outcomes and patient satisfaction among selected

women determined to be low risk for adverse birth outcomes. The extensive inclusion and exclusion criteria, including required initiation of prenatal care in the first trimester of pregnancy, limited the potential relevance of this large trial. Generally, women presenting for prenatal care in the first trimester of pregnancy differ from those presenting at later times, tending to have higher socioeconomic status, more planned pregnancies, and higher rates of health insurance.^{138,139} Even in this study conducted among insured women, 17 percent of women presenting for care were excluded because they made their first prenatal care visit after 13 weeks. The applicability of the study, conducted more than 20 years ago, in the context of updated diagnostic criteria and treatment algorithms may be limited for current clinical practice settings and populations. The study does, however, represent an important attempt to provide evidence for a specific screening approach relative to standard care.

Two fair-quality studies reporting on rates of adverse events with different screening protocols did not identify any harms of preeclampsia screening (**Table 7**). The 1996 trial of reduced prenatal visits found that preeclampsia diagnoses and related adverse outcomes did not differ with fewer screening visits. The difference in the number of visits between the two groups ultimately was not as large as the study had aimed to generate, however, and the study's age limits its value for current populations and practices. The study was also underpowered to detect rare but serious health outcomes related to preeclampsia. The other study¹¹⁵ provided some reassurance that there is no harm associated with a change in protocol when point-of-care urine tests are conducted for specific indications rather than on a routine basis, resulting in fewer tests on average. The before-after study design was subject to more potential threats to bias, including secular trends across the study period, than a randomized study. Reported differences in the study groups would tend to bias results in a conservative direction—toward worse preeclampsia-related outcomes in the indicated testing group—but this was not observed.

Effectiveness of Routine Screening for Preeclampsia Detection

No studies directly evaluated the test accuracy of blood pressure or urine protein screening for detecting preeclampsia. In a screening test performance paradigm, evidence to answer KQ 4 would compare results from screening blood pressure measurements and protein urine tests with confirmatory gold standard diagnostic tests. These data would populate a test accuracy table for assessing sensitivity and specificity of the individual or combined use of these screening tests for detection of preeclampsia. Since screening for preeclampsia is ongoing throughout pregnancy and provided at multiple time points, screening test accuracy must consider the timing of the test, cumulative clinical results, or both. A single positive proteinuria screening test is followed up with other diagnostic tests and, if the result is not confirmed, routine screening continues. Estimating how often false-positive and false-negative readings occur for elevated blood pressure and proteinuria has not been a research priority, likely owing to the low-resource nature of the screening tests and the low risk to patients of the confirmatory tests (e.g., additional blood pressure measurements, repeat point-of-care urine tests, diagnostic urine tests).

Although multiple studies have tested the associations of continuous elevated levels of blood pressure and proteinuria with the likelihood of developing preeclampsia at future time points in pregnancy, these do not directly address questions about screening test effectiveness in detecting preeclampsia. High blood pressure is an important sign of preeclampsia,⁴⁴ hence the importance

of the current clinical practice of repeat measurement at clinical visits. The accuracy of individual blood pressure readings is optimized if conducted in accordance with guidance on clinical blood pressure measurement in general and during pregnancy.^{140,141}

There is less evidence to support the relationship between proteinuria levels and adverse preeclampsia outcomes.^{5,142} Recent changes to the ACOG guidelines regarding the role of protein urine screening in the definition and management of preeclampsia highlight the importance of other signs and symptoms that might be used to diagnose preeclampsia in the absence of proteinuria.¹ Because the disease is not well understood and unexpected cases of preeclampsia that are not preceded by high blood pressure do occur, in the absence of an alternative evidence-based screening strategy, this historically important and relatively inexpensive aspect of prenatal health care will likely continue. We found no evidence of harms and no evidence to evaluate whether the use of one type of urine protein screening test versus another contributes to improved pregnancy outcomes.

Accuracy of Urine Screening Tests for Proteinuria

Most of the available evidence assessed how well point-of-care urine protein screening tests detect proteinuria, a diagnostic criterion for preeclampsia diagnosis, compared with the 24-hour collection gold standard. The most commonly studied test was the protein:creatinine test, which has been cited in recent diagnostic criteria as a reasonable alternative to 24-hour urine collection.^{1,143} The range of sensitivity and specificity was wide, and heterogeneity was high; sensitivity and specificity near 80 percent for studies using thresholds at or near 30 mg/mmol likely represents a best case scenario, but the high and largely unexplained heterogeneity limits conclusions. In routine prenatal care for women presenting outside of monitored study conditions, performance could be considerably lower and is likely to be more variable across clinical settings given the diversity in the tests available and 24-hour test assays. Our findings on the protein:creatinine test are consistent with those conducted by others in recent years.^{75,142} A review by Côté et al concluded that although this test was not sufficiently accurate to replace the 24-hour test for diagnostic confirmation, it does perform well enough to serve as a screening test to rule out significant proteinuria (excretion threshold of 0.3 g/day).⁷⁵

Based on relatively limited evidence available on other point-of-care tests, quantitative rather than qualitative readings of various urine dipstick tests appear more accurate.⁹⁴ In two studies, quantitative albumin:creatinine urine testing could obtain sensitivity and specificity in ranges similar to those of protein:creatinine tests. These two studies' populations exhibited a very different prevalence of proteinuria; one had less than 10 percent¹⁰⁶ and the other had nearly 50 percent of participants with significant proteinuria, according to the 24-hour test.⁹⁴ In both studies, however, albumin:creatinine testing had higher sensitivity and specificity values than those reported in studies of the protein:creatinine test. As in our own review, another recent review noted the limited evidence but also the potential promise of the albumin:creatinine test, deeming the test deserving of further investigation.¹⁴²

Evidence on test performance of point-of-care urine screening tests is both statistically and clinically heterogeneous. Different assays for the 24-hour reference test, manufacturers of test kits and readers, laboratory procedures, and protocols for collection and reading of the index and

gold standard tests could all contribute to the range of sensitivity and specificity observed. We sought to identify potential patterns in test performance based on these methodological characteristics but found few clear signals. The degree of spectrum bias, which is based on the extent to which preeclampsia was suspected, may have contributed to the heterogeneity in sensitivity, but the heterogeneity in specificity could not be explained. Limited information on the types of index tests and 24-hour assays used did not permit us to examine the role of different tests and procedures in performance.

None of the proteinuria test accuracy studies were conducted in a general primary care screening population of pregnant women. Instead, all of the available evidence was from pregnant women in the later part of the third trimester already identified with suspected preeclampsia and undergoing evaluation or diagnostic confirmation (**Table 7**). Tested populations were also predominantly white, further limiting the applicability of this review to women who bear a disproportionate burden of preeclampsia-related morbidity and mortality. Thus, the test accuracy estimates are subject to spectrum bias, wherein the higher pretest probability for the condition results in higher test performance.⁹⁶ Furthermore, nine of the studies included were conducted among inpatients, where the fidelity to collection protocols is higher than that in routine outpatient care, where problems with 24-hour gold standard tests have been well articulated.^{144, 145} Incomplete collection and erratic patterns of protein excretion can influence test accuracy results, making the clinical feasibility and reliability of the standard not entirely “golden.” It is likely that the test performance results we obtained are an upper boundary for performance and that studies in general or high-risk populations that do not already have a positive screen result would be more informative.

Considered broadly, protein urine screening occurs throughout pregnancy and false-positive results may lead to greater surveillance or further confirmatory testing. As noted in the review by Morris et al,¹⁴² the implications of the sensitivity and specificity of tests depend on the clinical actions taken with positive and negative results. Additionally, test performance for both would likely improve when cumulative rather than single test performance is considered, as false-negative readings can later be identified as positive and false-positive findings become subject to disconfirmation with followup testing. Thus, maximizing single-test performance for a relatively inexpensive and noninvasive test has limited value.

Effectiveness of Risk-Based Screening

We did not identify any studies that assessed the performance of different preeclampsia screening strategies with high- or low-risk women or compared screening effectiveness between women considered to be at high or low risk. We reviewed multivariable risk prediction models that could be useful for risk-based screening approaches or for targeting other clinical preventive services, such as aspirin prophylaxis for preeclampsia prevention. We identified 16 models externally validated in four studies that assessed the performance of multivariable risk assessment tools for use in pregnancy before 20 weeks’ gestation (**Table 7**). Of the five models found to have good or better discrimination based on the c-statistic, two had high detection (10% false-positive rate), but all models had low PPVs. Importantly, information on model calibration was not provided for any of the risk prediction models, and we could not determine the likely performance or impact of the available validated risk prediction models that would be expected

in routine clinical use. Two recent systematic reviews,^{146,147} several methodological critiques,^{90, 148-150} and recent guidance from ACOG¹³⁴ support our assessment of the current state of the evidence aimed at developing a model for preeclampsia risk prediction.

Our review identified one small, fair-quality prospective cohort study that evaluated potential psychological harms of preeclampsia risk assessment using a multivariable risk assessment model (**Table 7**) and found no difference in anxiety before and after clinical risk assessment.¹⁰² A recent qualitative study, which analyzed in-depth interviews with women who had been identified as low or high risk using a published risk assessment tool,¹⁵¹ found that some women had strong negative perceptions of being labeled at high risk.¹⁵² We did not find any evidence on harms related to risk assessment for health or pregnancy outcomes.

Owing partly to the rarity and complexity of preeclampsia and partly to limitations in methodological rigor, the current evidence for preeclampsia risk prediction does not support conclusions regarding likely performance, benefits, or harms. Recent efforts to establish reporting guidelines for prediction models and the growing maturity of risk assessment in other clinical areas will likely improve efforts to develop and validate risk prediction tools for preeclampsia.⁸⁵ All of the models we identified included clinical tests that are not routinely collected for all pregnant women in early pregnancy. While the collection of serum marker data might be feasible in the context of aneuploidy screening, first-trimester ultrasound scans to calculate the uterine artery pulsatility index for those who seek it are not currently recommended in routine prenatal care. The additional resources needed to conduct clinical tests and calculate risk might be worthwhile if there was a clear net benefit of a risk assessment tool relative to usual practice, where current risk assessment recommendations are based on established risk factors and the clinician's judgment.

Evaluating Clinical Performance of Preeclampsia Risk Prediction

To inform clinical practice, determining the net effect of risk assessment and the clinical actions that follow is necessary.¹³³ High sensitivity may be more important for preeclampsia risk assessment because false-negative results could be more detrimental than false-positive results;¹⁴⁹ a lower risk threshold, lower PPV, and possibly low-dose aspirin prophylaxis may be reasonable to consider for heightened surveillance.¹⁵³ Harms could occur among women misclassified as low risk, not offered aspirin prophylaxis, or assigned to lower-intensity prenatal care schedules. Heightened surveillance and allocation of aspirin to women at low risk for the disease could also lead to harms.

In the absence of studies comparing model-based risk assessment with usual care risk assessment, it is not clear whether a formal risk assessment algorithm would improve performance or health outcomes beyond currently recommended risk assessment practice.^{133,135, 154} The USPSTF has issued an evidence-based recommendation (grade B) for the use of low-dose aspirin (81 mg/day) to prevent preeclampsia and its associated morbidity and mortality.^{46,155} The recommendation specifies that benefits relative to potential harms are observed for women at increased risk of preeclampsia. The USPSTF, like NICE, provides a list of risk factors to assist clinicians in determining which patients are at elevated risk for preeclampsia (**Table 2**). These risk factors are based on the strongest epidemiologic associations and the most common risk

factors used to select high-risk participants in trials of aspirin for the prevention of preeclampsia. These approaches to risk stratification might be improved on with further development of validated tools for combining individual risk factors into an algorithm to provide more personalized risk assessment, but as we noted above, no externally validated models we evaluated provided evidence of performance that supports their clinical use.

Comparing risk prediction model effectiveness with NICE and USPSTF clinical risk assessment criteria would help provide a means of evaluating relative performance and whether incremental gains are worth implementation costs.^{135,154} We identified a few risk prediction models that compared detection in the proposed model with detection that would be achieved for the same population using the NICE criteria^{65,156-158} based on maternal characteristics and maternal history (**Table 2**). A recent study by Wright et al reported better detection using a new (but not yet externally validated model) compared with the NICE guidelines for risk stratification.¹⁵⁶ Although detection was higher with the model than with the NICE criteria (67% vs. 58%), models derived and tested in the same dataset tend to overestimate discrimination, and the observed difference may not be reproduced in external validation. We did not identify any studies comparing model performance with the risk factors in the USPSTF clinical considerations for assessing risk for purposes of low-dose aspirin prophylaxis.⁴⁶

Another risk prediction model recently reported by Macdonald-Wallis et al employed two different general population cohorts to establish a model for predicting preeclampsia, preterm birth, and SGA neonates.¹⁵⁹ The study more closely adhered to TRIPOD guidance for development and reporting of prediction modeling results, including provision of calibration plots for their best performing model. Because our review was scoped to identify models for use in the first half of pregnancy, this study was not included because the optimal model in external validation, for which calibration, recalibration, and classification were reported, included measures added to the model at 28 weeks' gestation and beyond. While not included in this review, our conclusions would not differ substantially with its findings. It does, however, represent an informative effort. First, the model proposed does not rely on serum markers or Doppler ultrasound measures, but instead uses common clinical history measures and an estimate of mean arterial pressure based on blood pressure measurements (i.e., SBP×2/DBP), which would be easily collected in primary care. Secondly, it is conceptually worthwhile to consider whether preeclampsia risk prediction might be beneficial on an ongoing basis across pregnancy, alongside screening. Clinicians may informally assess risk at each prenatal care visit based on the signs and symptoms they observe—with more or less concern that the patient is likely to develop preeclampsia, and decisions regarding additional visits or screening tests informed by these evaluations. The results of this model validation study do not provide evidence on how the proposed model would improve on current approaches.

The levels of discrimination and classification achieved with the proposed models are modest until adding the measurement of mean arterial pressure at 28 weeks' gestation, at which point the AUC is greater than 0.80 (c-statistic, 0.84 [95% CI, 0.79 to 0.88]).¹⁵⁹ The AUC is highest when mean arterial pressure at 36 weeks is added to the model (0.88 [95% CI, 0.84 to 0.93]). Model calibration and recalibration plots and classification tables are reported for the model that includes the 28 weeks mean arterial pressure measurement. Similar to the included models in our review, the PPV was very low. Although models using the same approach were developed to

predict preeclampsia-related health outcomes (i.e., preterm birth and SGA neonates), they had lower performance than for prediction of preeclampsia.

Despite better adherence to rigorous conduct and reporting of model development and validation, including a recalibrated model based on calibration plot observations, the clinical implications of the model remain unclear. The study authors conclude that the model could be used to risk stratify the clinical care of women who need more intensive monitoring from those likely to have a normal pregnancy. Whether the model would improve on current practices for adjusting the intensity of prenatal monitoring is unknown, however, since blood pressure readings at prenatal visits already serve as a key indicator of the need for closer monitoring. An accompanying editorial questioned what would be gained or lost with reduced monitoring that might be proposed for women with a low risk score using the model, particularly given other activities that occur in prenatal visits.¹⁵⁰ Conversely, there is an absence of information on the harms of risk prediction that could occur for the many women unnecessarily assigned to heightened surveillance given the high false-positive rates of the prediction model. Without comparisons of proposed models with current clinical practices, the potential benefits and harms of risk prediction cannot be determined, even with clear reporting of validated models. Testing different prenatal care algorithms against usual care, possibly incorporating use of the best performing and most feasible models, would be valuable to the field.

An example is a nonrandomized impact study conducted by Park et al¹¹⁸ that tested whether risk prediction Model A would improve the clinical process for assigning women at high risk for preeclampsia to low-dose aspirin prophylaxis to improve health outcomes. The simulation resulted in a statistically significant reduction in early-onset preeclampsia cases (12 vs. 1 case; $p=0.01$). The findings are encouraging but are limited by substantial, unexplained differences in the demographic characteristics of the two cohorts that could introduce confounding. Secular changes over the study time period (April 2010 to June 2013) might also have influenced the results, as would the approaches to risk assessment and aspirin prophylaxis in the original comparison cohort. Similar work to assess the clinical impact of risk prediction tools using randomized study designs should be pursued, ideally, with comparisons with current usual care.

Applicability

The only study we identified that compared different screening strategies in a randomized study was conducted more than 20 years ago in a large health maintenance organization. In the context of updated diagnostic criteria and management protocols for preeclampsia, application of this study to current clinical practice settings and populations is limited.

We did not identify any studies assessing the accuracy of urine protein tests in general prenatal care populations nor for the common practice of repeated testing over the course of pregnancy. The role of urine protein in the detection and diagnosis of preeclampsia is undergoing reevaluation as new guidelines and understanding of the disease process emerge. This may warrant consideration of different approaches to screening for women with hypertension in the absence of proteinuria in future reviews, as evidence accrues on the use of newer diagnostic criteria.

Limitations of the Review

The absence of rigorous studies on different approaches to preeclampsia screening, including risk-based approaches to care, is the most notable limitation. Newer studies are needed, in the current population of prenatal care patients with higher prevalence of obesity and other preeclampsia risk factors, to improve the evidence base for conducting screening. Moreover, with recent changes to diagnostic criteria, additional screening tests for women with hypertension but not proteinuria require study to estimate potential clinical benefits, harms, and performance and to develop evidence-based approaches to screening.¹⁶⁰

One reason for the absence of data on the test performance of screening with blood pressure and urine protein tests is the fact that these have until very recently also been the primary diagnostic criteria for the condition; thus, repeat tests to confirm initial readings are commonly conducted. The need to evaluate the proportion of women misclassified as having or not having preeclampsia at a single point in time, or even over the course of pregnancy, may be less important when the result of a false-negative is to continue screening, and the result of a false-positive is enhanced surveillance, also resulting in continued screening. The complexity of the condition and the limited tools currently available for screening may have necessarily focused scientific resources on efforts to better understand the pathogenesis and potential new disease markers. Advances in proteomics and genomics may yield better precursors and markers, as well as new treatments for preeclampsia.¹⁶¹⁻¹⁶⁴

Multivariable risk prediction tools that have been developed have aimed to combine serum tests and ultrasonography measures with known clinical history risk factors. Only recently have efforts been undertaken to combine a more robust set of known maternal history risk factors into a prediction model,¹³⁶ and this work has not yet been externally validated. Very large cohorts are needed to develop and test models for early-onset preeclampsia, when the risk of poor outcomes is greatest. Many of the studies we identified had very few cases to classify, so the CIs for performance estimates were wide. There are shortcomings in the literature on preeclampsia prediction modeling in transparency and completeness of reporting, as noted by others.^{90,146} In particular, the absence of calibration statistics limited our ability to comprehensively evaluate and compare model performance.¹⁴⁸ AUC values do not provide a solid basis for determining how well, and at what level of risk, a risk prediction model would perform.¹⁶⁵

Eleven included studies were pooled for meta-analysis of the accuracy of urine tests for protein:creatinine, with results indicating high, mostly unexplainable heterogeneity, which limited our ability to generalize the accuracy of test performance. Heterogeneity was due in part to the degree to which preeclampsia was suspected. A recent methodological review for diagnostic studies noted limitations in the methods for determining the overall degree of heterogeneity in test accuracy studies, in part because of the interrelatedness of sensitivity and specificity.⁹⁶ The bivariate random-effects model can take these correlations into account, but interpretation is challenging and better approaches are needed.

Future Research Needs

The complexity of preeclampsia and the variety of ways it can present with regard to timing, signs, and symptoms make it difficult to identify a highly effective and broadly applicable risk assessment and screening strategy.¹⁰ Studies aimed at testing risk assessment and screening algorithms are needed to provide a more robust evidence base with which to inform prenatal care screening practices. Large study populations are required to compare different approaches to screening and effects on maternal and perinatal health outcomes, as well as longer-term sequelae. Basic descriptive studies characterizing variations in current preeclampsia screening practices in different types of health care settings would be helpful for identifying alternative screening approaches to evaluate in clinical studies. Basic research into the pathophysiology of preeclampsia will also help identify better tools for risk assessment and screening. If preeclampsia is comprised of several distinct syndromes,¹⁶⁶ new screening approaches will need to be developed to distinguish subtypes, especially those most likely to result in serious morbidity or mortality without intervention. If, as others have proposed,^{156,167} preeclampsia is a single condition with a spectrum of severity and speed of progression, it will remain important to identify the best tools and clinical protocols for capturing all cases as soon as they arise for enhanced monitoring and evidence-based treatment protocols. Additional risk assessment measures in the second half of pregnancy may further predict the likelihood of developing disease. For example, uterine artery Doppler measurement in later pregnancy^{168,169} and serum uric acid levels¹⁷⁰ are potentially useful for identifying women at risk for adverse outcomes resulting from preeclampsia. Future validation of these techniques may help guide more individualized surveillance of women at highest risk.

Protein dipstick tests are an initial screening for preeclampsia in many health care settings and are used for diagnosis when other tests are not available. Urine dipstick tests for proteinuria have poor test performance,¹⁷¹ particularly with visual rather than automated readings.^{94,172} Further research on the extent to which these tests are used to guide clinical decisionmaking and whether variations in practice explain differences in health outcomes could inform investigations into best practices. Assessing the protein:creatinine ratio in point-of-care urine samples appears to have more evidence suggestive of better performance, but further evaluation of accuracy in general populations, and with repeat testing, could better estimate its optimal role for proteinuria detection for routine preeclampsia screening.

Recently published models based on maternal characteristics and clinical history may hold promise if external validation supports their reproducibility.^{136,156} These studies have focused on a larger set of health behaviors, clinical measurements, health history, and maternal characteristics. A model developed by North et al¹³⁶ in the international cohort study Screening for Pregnancy Endpoints (SCOPE) sought a clinical tool for risk prediction for use at around 15 weeks' gestation in nulliparous women, based on clinical risk factors that could be easily collected in routine care. Based on an international cohort of healthy nulliparous women from New Zealand, Australia, the United Kingdom, and Ireland (n=3,529), the study methods more closely aligned with TRIPOD guidance. Overall, 5 percent of the cohort developed preeclampsia. The performance of the model was modest (c-statistic, 0.71) but was adjusted statistically with a 10-fold cross-validation technique to adjust for optimism/overfitting bias. Unlike the existing models we identified, the SCOPE model considered a larger set of potential predictors and found

some predictive factors that were not included in previous algorithms, such as family history of coronary heart disease, vaginal bleeding during pregnancy for at least 5 days, and protective factors that decreased risk (e.g., high fruit intake, prior miscarriage with the same partner).

Given the heterogeneity of the disease, screening tools aimed at different subtypes of preeclampsia, once they are more clearly defined, and for different study populations, may be necessary. The SCOPE model would not be applicable to parous women entering prenatal care, but the majority of cases of preeclampsia occur among nulliparous women. Efforts to test and recalibrate a clinically feasible tool for other targeted or broader populations could be undertaken. Well-designed impact studies are needed to determine what level of performance improves on current clinical risk assessment practices using to compare usual care with more complex risk prediction model-based tools. Without these impact studies, the value of new instruments for improving processes of care and health outcomes cannot be quantified.

Conclusion

There is limited evidence available to determine the health benefits and harms of preeclampsia screening or the test performance of different screening and risk assessment strategies over the course of pregnancy. Despite the lack of empiric evidence, routine preeclampsia screening as currently conducted in prenatal care (i.e., blood pressure measurement and urine protein testing as part of routine pregnancy monitoring) is an established and feasible practice that is unlikely to be harmful or expensive. This is particularly true since the result of a positive screening measurement is repeat or similar testing for diagnostic confirmation and determination of severity to inform management. For most cases that will not develop into severe preeclampsia, enhanced monitoring is the most common initial clinical management. Given the rarity of preeclampsia and the potentially devastating consequences, especially in early-onset disease requiring preterm delivery, the focus of scientific inquiry has emphasized understanding the complex condition to more accurately identify those who will develop severe disease.

The complex pathophysiology of preeclampsia and its diverse outcomes present challenges for research aimed at improving health outcomes through evidence-based risk assessment and screening strategies. Research on the effectiveness of longstanding screening practices may be a lower research priority relative to efforts to better define the condition; to understand its physiological and causal underpinnings; and to develop new markers, tools, or tests for early identification and disease treatment. Broadly considered, screening recommendations for preeclampsia, including prior USPSTF guidance, highlight the low resource requirements of screening for high blood pressure and proteinuria. Efforts to identify the patients most likely to have severe or early-onset preeclampsia hold promise for better targeting of enhanced screening and preventive interventions. None of the existing validated models to estimate preeclampsia risk are sufficiently supported by evidence of performance that would warrant clinical application to general populations of pregnant women. Additional development, validation, and implementation research is needed to derive a tool ready for preeclampsia risk assessment in routine prenatal care and define its uses for improving health outcomes.

Periodic blood pressure and proteinuria measurements are routinely collected in primary

obstetric care. Because of the long history of use of blood pressure and urine protein screening for preeclampsia screening, few studies have assessed their benefits and harms. Changes to diagnostic criteria in conjunction with evolving evidence on preeclampsia pathophysiology may foster new opportunities for improving clinical practice.

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Figure 1. Analytic Framework

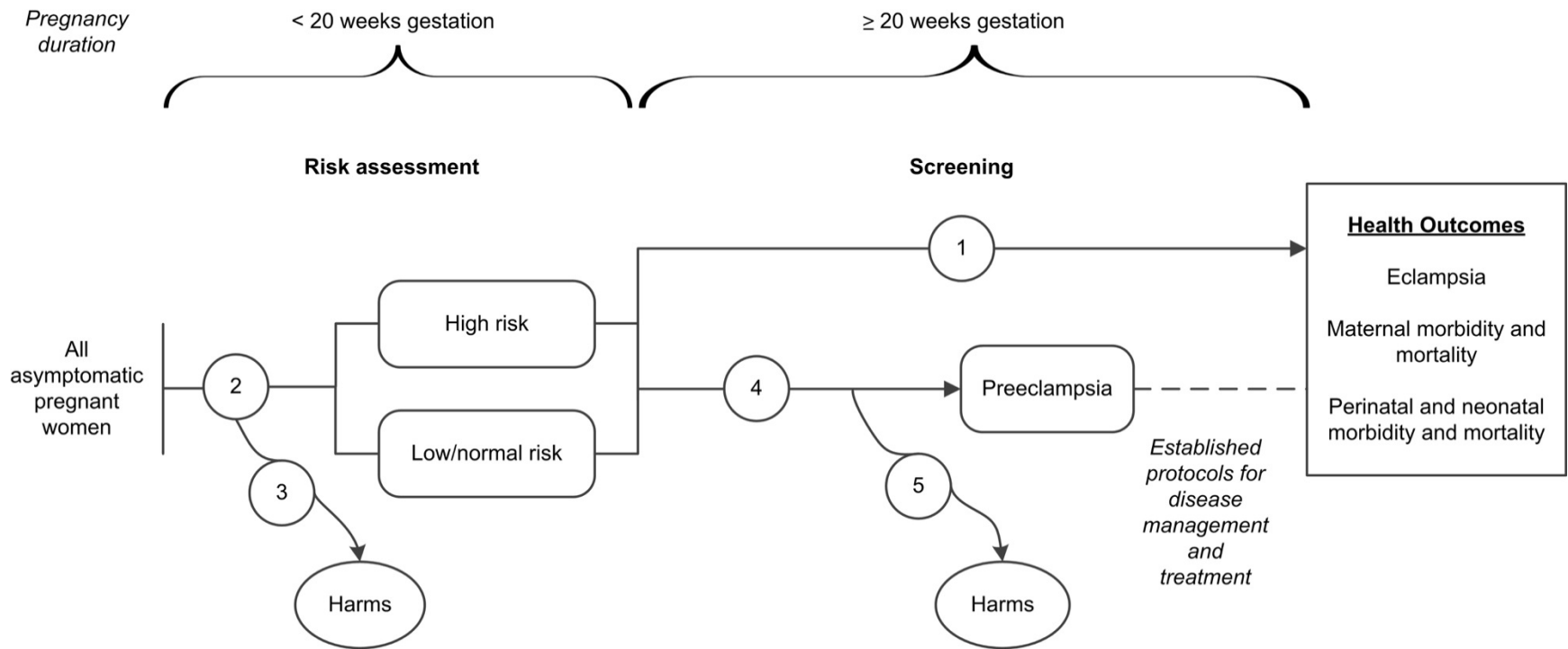
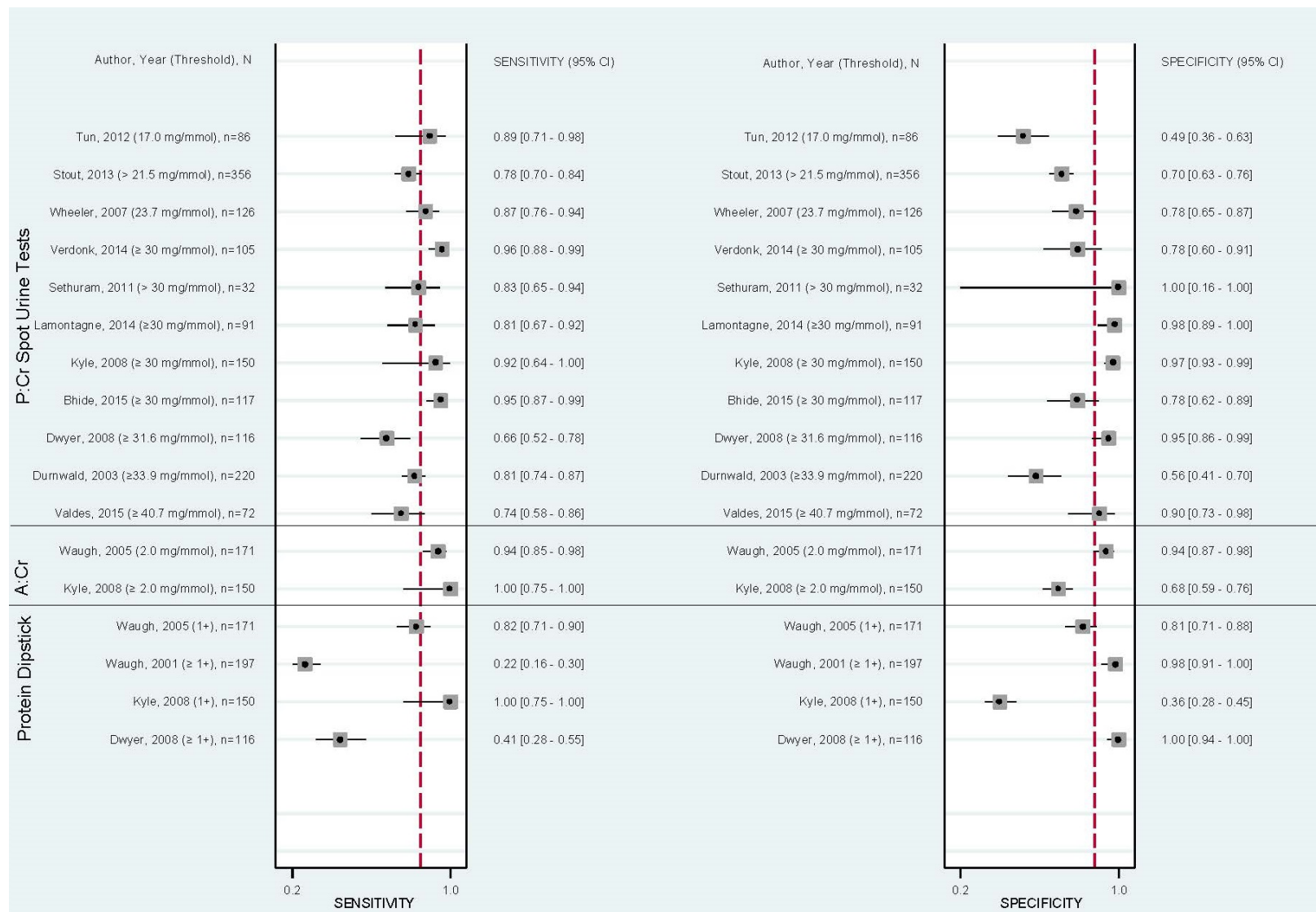


Figure 2. Diagnostic Accuracy of Point-of-Care Tests for Proteinuria (Key Question 4a)



Note: One study¹¹⁴ is not plotted as it did not provide enough information to determine a 2x2 table.

Abbreviations: A=albumin; CI=confidence interval; Cr=creatinine; P=protein.

Table 1. Recent Recommendations for Preeclampsia Screening

Organization	Year	Recommendation
Society of Obstetricians and Gynecologists of Canada (SOGC) ¹⁴³	2014	<p>The diagnosis of hypertension should be based on office or in-hospital BP measurements. (II-B; Low/Strong) <i>[Additional detailed recommendations for blood pressure measurement and diagnosis are provided.]</i></p> <p>All pregnant women should be assessed for proteinuria. (II-2B; Low/Weak) <i>[Comments: We suggest screening with urinary dipstick at each antenatal visit. Proteinuria should be quantified by PrCr or 24h collection if preeclampsia is suspected.]</i></p> <p>Significant proteinuria should be suspected when urinary dipstick proteinuria is $\geq 1+$. (II-2A; Moderate/Strong)</p> <p>Screening using biomarkers or Doppler ultrasound velocimetry of the uteroplacental circulation cannot be recommended routinely at present for women at low or increased risk of preeclampsia until such screening has been shown to improve pregnancy outcome. (II-2C; Very low/Weak)</p>
American Congress of Obstetricians and Gynecologists (ACOG) ¹	2013	Specific preeclampsia screening recommendations are not provided (e.g., type or frequency of screening tests to use); guidelines are primarily focused on diagnostic criteria and disease management.
National Institute of Health and Care Excellence (NICE) ⁴⁷	2008	Blood pressure measurement and urinalysis for protein should be carried out at each antenatal visit to screen for preeclampsia.
Royal College of Obstetricians and Gynaecologists (RCOG) ¹⁷³	2003	<p>All women with blood pressure $>140/90$ mm Hg, with or without proteinuria, should be referred to a day assessment or obstetric unit. (Grade A)</p> <p>All women with persistent proteinuria, even in the absence of hypertension, should be referred for further investigation. (Grade A)</p> <p>Although pregnancies associated with an abnormal uterine artery Doppler waveform are at significant risk of adverse outcome (particularly severe preeclampsia requiring early delivery), its introduction as a screening test for all women cannot currently be recommended other than in clinical trials. (Grade B)</p> <p>Automated instruments for BP measurement are generally not validated for use during pregnancy and preeclampsia. Therefore, the use of mercury sphygmomanometers remains preferable. (Grade B)</p> <p>Due to the variation in urine concentration, largely determined by hydration, all urine screening in obstetric day units should be by protein:creatinine ratio; this can be by laboratory test or at point of care. (Grade C)</p> <p>The definition of gestational proteinuria is derived from studies calculating the 95th centile for an uncomplicated population. A protein loss of >300 mg in 24 hours is associated with an increased morbidity to the mother and her baby. (Grade B)</p>
U.S. Preventive Services Task Force (USPSTF) ⁷⁴	1996, reaffirmed 2002 No longer posted – out of date	Screening for preeclampsia with blood pressure measurement is recommended for all pregnant women at the first prenatal visit and periodically throughout the remainder of the pregnancy. Further diagnostic evaluation and clinical monitoring, including frequent BP monitoring and urine testing for protein, are indicated if BP does not decrease normally during the middle trimester, if the SBP increases 30 mm Hg above baseline, if the DBP increases 15 mm Hg above baseline, or if the blood pressure exceeds 140/90 mm Hg above baseline. (B recommendation)

Abbreviations: BMI=body mass index; BP=blood pressure; DBP=diastolic blood pressure; SBP=systolic blood pressure.

Table 2. Factors for Clinical Assessment of Preeclampsia Risk*

American Congress of Obstetricians and Gynecologists (ACOG) ¹	USPSTF Risk Assessment for Low-Dose Aspirin Prophylaxis ⁴⁶	National Institute of Health and Care Excellence (NICE) ⁴⁷
<p><i>Risk factors</i></p> <p>Primiparity Previous preeclamptic pregnancy Chronic hypertension, chronic renal disease, or both History of thrombophilia Multifetal pregnancy In vitro fertilization Family history of preeclampsia Type 1 or 2 diabetes mellitus Obesity Systemic lupus erythematosus Advanced maternal age (age >40 years)</p>	<p><i>High risk</i>[†]</p> <p>History of preeclampsia Multifetal gestation Chronic hypertension Type 1 or 2 diabetes Renal disease Autoimmune disease (i.e., systemic lupus erythematosus, antiphospholipid syndrome)</p> <p><i>Moderate risk</i>[‡]</p> <p>Nulliparity Obesity (BMI >30 kg/m²) Family history of preeclampsia Sociodemographic characteristics (African American race, low socioeconomic status) Age ≥35 years Personal history factors (e.g., low birth weight or small for gestational age, previous adverse pregnancy outcome, >10-year pregnancy interval)</p> <p><i>Low risk</i></p> <p>Previous uncomplicated full-term delivery</p>	<p><i>High risk</i>[†]</p> <p>Hypertensive disease during previous pregnancy Chronic hypertension Type 1 or 2 diabetes Chronic kidney disease Autoimmune disease (i.e., systemic lupus erythematosus, antiphospholipid syndrome)</p> <p><i>Moderate risk</i>[‡]</p> <p>First pregnancy Obesity (BMI ≥35 kg/m²) Family history of preeclampsia Age ≥40 years Pregnancy interval >10 years Multiple pregnancy</p>

* Includes only risk factors that can be obtained from the patient medical history. Clinical measures, such as uterine artery Doppler ultrasound, may additionally be used by some clinicians to evaluate risk.

† The USPSTF and NICE recommend low-dose aspirin if the patient has ≥1 high-risk factors.

‡ The USPSTF recommends considering low-dose aspirin if the patient has several of the listed moderate-risk factors. NICE recommends low-dose aspirin if the patient has at least two moderate-risk factors.

Abbreviations: BMI=body mass index.

Table 3. Differences in Health Outcomes During Pregnancy, at Time of Delivery, or 6 Weeks Postpartum (Key Questions 1a and 5)

Study, Quality	Category	Outcomes	Group	Results	Between-Group Difference
McDuffie, 1996 ⁹⁷ Fair	Preeclampsia	Mild PE, n (%)	IG	59 (5.1)	RR, 0.94 (95% CI, 0.78 to 1.14); p=0.74
			CG	66 (5.7)	
		Severe PE, n (%)	IG	10 (0.9)	RR, 1.05 (95% CI, 0.68 to 1.62); p=0.41
			CG	9 (0.8)	
	Preterm birth	Preterm delivery <32 weeks, n (%)	IG	10 (0.9)	RR, 1.11 (95% CI, 0.73 to 1.68); p=0.32
			CG	8 (0.7)	
		Preterm delivery <37 weeks, n (%)	IG	73 (6.3)	RR, 1.08 (95% CI, 0.92 to 1.27); p=0.19
			CG	63 (5.4)	
	Delivery complications	Abruptio placentae, n (%)	IG	17 (1.5)	RR, 1.21 (95% CI, 0.90 to 1.64); p=0.13
			CG	11 (0.9)	
		Apgar score at 5 minutes <7, n (%)	IG	18 (1.6)	RR, 0.77 (95% CI, 0.53 to 1.10); p=0.95
			CG	29 (2.5)	
		Chorioamnionitis, n (%)	IG	9 (0.8)	RR, 0.90 (95% CI, 0.55 to 1.46); p=0.68
			CG	11 (0.9)	
		Placenta previa, n (%)	IG	7 (0.6)	RR, 0.87 (95% CI, 0.50 to 1.52); p=0.70
			CG	9 (0.8)	
	Postpartum hemorrhage with cesarean delivery, n (%)	IG	2 (1.3)	RR, 0.77 (95% CI, 0.26 to 2.27); p=0.77	
		CG	3 (2.2)		
	Postpartum hemorrhage with vaginal delivery, n (%)	IG	32 (3.2)	RR, 0.98 (95% CI, 0.77 to 1.27); p=0.47	
		CG	33 (3.2)		
	Preterm labor, n (%)	IG	79 (6.8)	RR, 1.01 (95% CI, 0.86 to 1.18); p=0.44	
		CG	77 (6.6)		
	Preterm premature rupture of membranes, n (%)	IG	38 (3.3)	RR, 1.00 (95% CI, 0.80 to 1.25); p=0.50	
		CG	38 (3.3)		
	Cesarean delivery	Cesarean delivery, overall, n (%)	IG	151 (13.0)	RR, 1.04 (95% CI, 0.93 to 1.17); p=0.25
			CG	140 (12.0)	
	Perinatal/neonatal mortality	Stillbirth, n (%)	IG	5 (0.4)	RR, 1.00 (95% CI, 0.54 to 1.86); p=0.50
			CG	5 (0.4)	
	Birth weight	Birth weight (g), mean (SD)	IG	3,286 (520)	NR; p=0.66
			CG	3,295 (536)	
		Very low birth weight (<1,500 g), n (%)	IG	7 (0.3)	RR, 1.08 (95% CI, 0.65 to 1.79); p=0.39
			CG	6 (0.3)	
Low birth weight (<2,500 g), n (%)	IG	64 (5.4)	RR, 0.94 (95% CI, 0.78 to 1.12); p=0.76		
	CG	72 (6.1)			
SGA, n (%)	IG	36 (3.1)	RR, 1.13 (95% CI, 0.91 to 1.41); p=0.16		
	CG	28 (2.4)			
Health care use during pregnancy	Total number of visits, mean (SD)	IG	12.0 (4.2)	NR; p<0.001	
		CG	14.7 (4.2)		
Satisfaction with prenatal care at 6 weeks postpartum	Number of prenatal visits, just right	IG	494 (89.2)	NR; p=0.002	
		CG	473 (82.8)		
	Number of prenatal visits, too few	IG	49 (8.8)	NR	
CG		6 (1.1)			

Table 3. Differences in Health Outcomes During Pregnancy, at Time of Delivery, or 6 Weeks Postpartum (Key Questions 1a and 5)

Study, Quality	Category	Outcomes	Group	Results	Between-Group Difference
		Number of prenatal visits, too many	IG	11 (2.0)	NR
			CG	92 (16.1)	
		Quality of prenatal care, excellent or good, n (%)	IG	574 (97.5)	NR; p=0.67
			CG	587 (97.8)	
Rhode, 2007 ^{11b*}	Preeclampsia	Preeclampsia/eclampsia, n (%)	IG	23 (2.3)	NR; p=0.001
			CG	36 (3.8)	
Fair	Preterm birth	Preterm delivery, n (%)	IG	50 (4.9)	NR; p=0.14
			CG	72 (7.7)	
	Cesarean delivery	Cesarean delivery, n (%)	IG	181 (17.8)	NR; p=0.029
			CG	173 (18.5)	
	Other maternal morbidity	Cystitis, n (%)	IG	33 (3.3)	NR; p<0.0001
			CG	15 (1.7)	
		Gestational diabetes, n (%)	IG	42 (4.2)	NR; p=0.82
			CG	81 (9.3)	
		Gestational hypertension, n (%)	IG	58 (5.7)	NR; p<0.0001
			CG	38 (4.1)	
		High blood pressure, n (%)	IG	81 (8.0)	NR; p=0.0005
			CG	74 (7.9)	
		Pyelonephritis, n (%)	IG	4 (0.40)	NR; p<0.0001
			CG	4 (0.40)	
		Asymptomatic bacteriuria, n (%)	IG	67 (6.8)	NR; p=0.051
			CG	79 (8.7)	
		Urinary tract infection, n (%)	IG	141 (14.2)	NR; p=0.043
			CG	140 (15.4)	

*Rhode, 2007 used statistical tests for noninferiority. A p-value <0.05 indicates rates are statistically equivalence (no greater than 0.04 in one direction).

Abbreviations: CG=control group; CI=confidence interval; IG=intervention group; NR=not reported; PE=preeclampsia; RR=relative risk; SD=standard deviation; SGA=small for gestational age.

Table 4. Study Characteristics of Preeclampsia Risk Prediction External Validation Studies (Key Question 2)

External Validation Studies	Oliveira 2014⁹⁹ Baltimore, MD PE requiring delivery: <34 weeks' gestation (early) ≥34 weeks' gestation (late)	Park 2013¹⁰⁰ Sydney, Australia PE requiring delivery: <34 weeks' gestation (early)	Skrastad 2014¹⁰¹ Trondheim, Norway PE requiring delivery: <37 weeks' gestation (early) <42 weeks' gestation (any) >34 weeks' gestation (late)	Farina 2011⁹⁸ Bologna, Italy PE diagnosis: >34 weeks' gestation
Study design	Prospective cohort	Prospective cohort	Prospective cohort	Prospective cohort
Study population	Women with singleton pregnancies	Women with singleton pregnancies presenting for aneuploidy screening	Nulliparous women	Women with singleton pregnancies enrolled at screening visit for early diagnosis of chromosomal and other fetal abnormalities, and delivery in tertiary care center
Study period	2007–2010	April 2010–March 2012	September 2010–March 2012	December 2007–April 2010
Sample size (n)	871–2,962 (model n depended on availability of variables needed for each predictive model)	3,066	541	554
Outcome prevalence (%)	Early PE: 1.0–1.2 (10–30 cases) Late PE: 4.1–5.0 (78–116 cases)	Early PE: 0.4 (12 cases)	Any PE: 3.9 (21 cases) Preterm PE requiring delivery (<37 wks): 0.9 (5 cases)	Late PE: 7.0 (39 cases)
Funding	Diagnostic Technologies Limited and PerkinElmer	NR	Norwegian University of Science and Technology; National Center for Fetal Medicine	Ricerca Fondamentale Orientata

Abbreviations: PE=preeclampsia; wks=weeks.

Table 5. External Validation Performance of Five Preeclampsia Risk Prediction Models With Good or Better Discrimination (c-statistic ≥ 0.80) (Key Question 2)

	MODEL A: Poon 2010^{127**††} London, UK	MODEL A: Poon 2010^{127**††} London, UK	MODEL B: Odibo 2011¹²² St. Louis, MO	MODEL C: Akolekar 2013¹²⁰ London and Gillingham, UK	MODEL D: Poon 2010^{127**††} London, UK	MODEL E: Onwudiwe 2008¹²³ London, UK
Cohort study for external validation of model	Oliveira 2014 ⁹⁹ Baltimore, MD	Park 2013 ¹⁰⁰ Sydney, Australia	Oliveira 2014 ⁹⁹ Baltimore, MD	Skrastad 2014 ¹⁰¹ Trondheim, Norway	Farina 2011 ⁹⁸ Bologna, Italy	Farina 2011 ⁹⁸ Bologna, Italy
Number of participants eligible for model validation cohort	2,833	3,014	871	541	554	554
PE timing*	PE requiring early delivery (<34 weeks)	PE requiring early delivery (<34 weeks)	PE requiring early delivery (<34 weeks)	PE requiring early delivery (<37 weeks)	Late PE diagnosis (>34 weeks)	Late PE diagnosis (>34 weeks)
% PE outcome (n cases)	1.0 (29 cases)	0.4 (12 cases)	1.2 (10 cases)	0.9 (5 cases)	7.0 (39 cases)	7.0 (39 cases)
c-statistic, [†] (95% CI)	0.80 (0.71–0.89)	0.93 (0.92–0.94)	0.86 (0.73–0.99)	0.94 (0.86–1.00)	0.93 (0.88–0.98)	0.85 (0.78–0.93)
Calibration [‡]	NR	NR	NR	NR	NR	NR
Detection, [§] % (95% CI)	52 (NR)	91.7 (61.5–98.6)	80 (NR)	80.0 (28.4–99.5)	84.6 (73.3–95.9)	74.4 (60.7–88.1)
PPV	4.2 (2.6–6.5)	3.6 (2.0–7.0)	11.3 (5.3–21.5)	6.8 (1.9–16.5)	39.3	36.3
NPV [¶]	99.6 (99.0–100.0)	99.9 (99.7–99.9)	99.8 (99.0–100.0)	99.8 (98.8–100.0)	98.7	97.9
Model variables	Race, chronic HTN history, conception mode, parity, MAP, PAPP-A, Doppler ultrasound uterine artery pulsatility index	Race, chronic HTN history, conception mode, parity, MAP, PAPP-A, Doppler ultrasound uterine artery pulsatility index	Chronic HTN, PAPP-A, PP13, Doppler ultrasound uterine artery pulsatility index	Age, weight, height, race/ethnicity, personal PE history, mother PE history, parity, mode of conception, chronic health conditions, MAP, PAPP-A, PIGF, Doppler ultrasound uterine artery pulsatility index	Age, BMI, race/ethnicity, mother PE history, parity, MAP, Doppler ultrasound uterine artery pulsatility index	BMI, race/ethnicity, parity, personal PE history, MAP, Doppler ultrasound uterine artery pulsatility index

* Preeclampsia defined as requiring delivery, with the exception of the Farina external validation study, which defined the outcome as the diagnosis of preeclampsia.

[†] A test performance statistic (equivalent to AUC) used to assess discrimination, a model performance measure that refers to how well a model differentiates between those with and without the outcome.⁸³

[‡] A model performance measure that refers to how well predicted risks compare with observed outcomes, preferably evaluated graphically by calibration plots and supplemented by a formal statistical test (the Hosmer-Lemeshow test for logistic regression and its equivalent for Cox regression).⁸³

[§] Analogous to sensitivity. The percent of cases correctly classified based on a predefined false-positive risk threshold.⁸³ Detection for preeclampsia in this table was based on a fixed 10% false-positive rate (risk cutpoint for 90% specificity), which was the most commonly reported.

^{||} A test performance statistic used to measure what proportion of patients who test positive have the disease; PPV not reported in the Farina external validation study and was calculated by hand.

[¶] A test performance statistic used to measure what proportion of patients who test negative do not have the disease; NPV not reported in the Farina external validation study and was calculated by hand.

** Derived from the Fetal Medicine Foundation Algorithm.

†† Clinical history algorithm described in Poon 2010⁶⁵ and Poon 2009.¹²⁸

Abbreviations: AUC=area under the curve; BMI=body mass index; CI=confidence interval; DBP=diastolic blood pressure; HTN=hypertension; MAP=mean arterial pressure; NPV=negative predictive value; NR=not reported; PAPP-A=pregnancy-associated plasma protein A; PE=preeclampsia; PIGF=placental growth factor; PPV=positive predictive value; SBP=systolic blood pressure.

Table 6. Index Tests and Reference Standard Characteristics of Included Diagnostic Accuracy Studies (Key Question 4a)

Study, Quality	Index Test (Make, Manufacturer)	Index Test Sampling Methods	Index Test Machine and Assay	Index Test Operator and Reader	24-Hour Ref Stand Collection Method	Ref Stand Machine and Assay	Ref Stand Operator and Reader
Index Test, Protein:Creatinine							
Tun, 2012 ¹¹⁰ Fair	P/Cr spot test (NR)	Number of samples: 1 Initial urine specimen (which was otherwise discarded). Some had it collected from the timed specimen (24-hour) or immediately after the timed collection.	NR NR	NR, sent to Health Network Laboratory	Started at time of admission; collected in 2 consecutive 12-hour collections; total protein a combination of both 12-hour urine specimens	NR ADVIA total protein urine assay (modified Fujita method)	NR, sent to Health Network Laboratory
Stout, 2013 ¹⁰⁹ Fair	P/Cr spot ratio (NR)	Number of samples: 1 Ratio assessment prior to initiation of 24-hour collection	NR Enzymatic creatinase	NR	First 24-hour urine collection was used for each patient.	NR Benzethonium chloride	NR
Wheeler, 2007 ¹¹³ Fair	P/Cr spot ratio (NR)	Number of samples: 1 Samples obtained at the beginning of the 24-hour urine collection	Johnson & Johnson Vitros 250 Biuret method (protein); 2-point rate method (creatinine)	NR	NR	NR NR	NR
Young, 1996 ¹¹⁴ Fair	P/Cr spot test (NR)	Number of samples: 1 Single voided specimen collected when patient emptied bladder to begin the timing of the 24-hour urine collection (in 66% of samples); otherwise, single voided sample collected after the completion of the 24-hour collection (34% of samples). No specimen collected as the first void of the morning.	Beckman analyzer Standard spectrophotometric technique	NR	No specimen collected as the first void of the morning.	NR NR	NR

Table 6. Index Tests and Reference Standard Characteristics of Included Diagnostic Accuracy Studies (Key Question 4a)

Study, Quality	Index Test (Make, Manufacturer)	Index Test Sampling Methods	Index Test Machine and Assay	Index Test Operator and Reader	24-Hour Ref Stand Collection Method	Ref Stand Machine and Assay	Ref Stand Operator and Reader
Verdonk, 2014 ¹¹¹ Good	P/Cr spot test (Albustix, Siemens Healthcare Diagnostics)	Number of samples: 3 Began at midnight with 5-mL aliquots saved for P/Cr testing from requested spontaneous voids at approximately 8 am, 12 pm (noon), and 5 pm; visually analyzed.	CREA plus, Roche Diagnostics Enzymatic assay (Cr), colorimetric assay (P)	NR	Began at midnight, nurses monitored for completeness and when errors occurred, the procedure was stopped and restarted at midnight the next day.	NR NR	NR
Sethuram, 2011 ¹⁰⁸ Fair	P/Cr spot test (NR)	Number of samples: 1 10-mL sample of urine collected before 24-hour collection; avoided the first void sample.	Abbott Diagnostics analyzer Benzethonium chloride turbidometric method (protein); Jaffe method (Cr)	NR	Avoided the first void sample.	Abbott Diagnostics analyzer Benzethonium chloride turbidometric method (protein)	NR
Lamontagne, 2014 ¹⁰⁷ Good	P/Cr spot ratio (NR)	Number of samples: 1 When women entered study, urinalysis, urine culture, and P/Cr calculated on same urine sample provided at any moment during the day before 24-hour urine collection; not collected with catheter.	Beckman Coulter multianalyzer with the Synchron LX system Colorimetric method using pyrogallol red-molybdate (P); Jaffe method (Cr)	NR	Inpatients instructed on how to proceed by a nurse, while ambulatory women given oral and written instructions; not collected with catheter.	Beckman Coulter multianalyzer with Synchron LX system Colorimetric method using pyrogallol red-molybdate (P); Jaffe method (Cr)	NR
Kyle, 2008 ¹⁰⁶ Fair	P/Cr spot test (NR)	Number of samples: 1 Aliquot from midstream urine specimen before 24-hour, performed at health laboratory	Abbott Ci8200 Analyzer NR	Research midwife	24-hour urine collection as an outpatient. Discard first void in the toilet and write date/time of the sample on the request form, all subsequent voids were collected. Final void collected 24 hours later and placed in the specimen container.	NR Benzethonium chloride assay	NR

Table 6. Index Tests and Reference Standard Characteristics of Included Diagnostic Accuracy Studies (Key Question 4a)

Study, Quality	Index Test (Make, Manufacturer)	Index Test Sampling Methods	Index Test Machine and Assay	Index Test Operator and Reader	24-Hour Ref Stand Collection Method	Ref Stand Machine and Assay	Ref Stand Operator and Reader
Bhide, 2015 ¹⁰³ Fair	P/Cr spot test (NR)	Number of samples: 1 Usually collected and sent to the laboratory on the day/time of presentation to day assessment unit (but if not, within 48 hours from attendance at no specific time of day), before 24-hour. Only data from the first attendance included in study.	NR Pyragallol red (protein), Jaffe kinetic method (Cr)	NR	24-hour urine collection	NR Pyragallol red (protein)	NR
Dwyer, 2008 ¹⁰⁵ Good	P/Cr spot test (NR)	Number of samples: 1 Obtained before 24-hour collection, taken immediately after 24-hour. All samples collected via clean catch unless the membranes had been ruptured, in which case specimens were captured by catheter.	Synchron LX Systems Pyrogallol red/molybdate (P) and Jaffe rate (Cr)	Laboratory technician	Most collected as outpatients, all samples collected via clean catch unless the membranes had been ruptured, in which case specimens were captured by catheter.	NR NR	Laboratory technician
Durnwald, 2003 ¹⁰⁴ Fair	P/Cr spot ratio (NR)	Number of samples: 1 Random urine collection before initiation of 24-hour collection	NR Biuret reaction; modified Jaffe reaction	NR	Outpatients collected all urine in a container for 24 hours and returned it to the outpatient laboratory; inpatients who had vaginal bleeding and/or active labor were receiving Mg sulfate seizure prophylaxis, those who had delivered collected by Foley catheter.	NR NR	NR

Table 6. Index Tests and Reference Standard Characteristics of Included Diagnostic Accuracy Studies (Key Question 4a)

Study, Quality	Index Test (Make, Manufacturer)	Index Test Sampling Methods	Index Test Machine and Assay	Index Test Operator and Reader	24-Hour Ref Stand Collection Method	Ref Stand Machine and Assay	Ref Stand Operator and Reader
Valdes, 2015 ¹¹⁹ Fair	P/Cr spot test (NR)	Number of samples: 1 Additional urine sample (15-20 mL) collected for storage at -20° C for quantification of P:Cr concentrations on completion of the study period	NR NR	NR	Upon admission, patients underwent a 24-hour proteinuria test.	NR NR	NR
Index Test, Albumin:Creatinine							
Waugh, 2005 ³⁴ Good	Dipstick Clinitek Microalbumin (automated) (Bayer)	Number of samples: 1 Early morning sample before the final 24-hour specimen was added to the 24-hour collection, a mixed 10-mL aliquot was removed for urinalysis.	Clinitek 50 Two semiquantitative immunoassays for albumin and Cr	NR	On waking, the first void was discarded and the sample started with the second urine specimen; the final specimen was the first void the following day.	NR Benzethonium chloride assay	NR
	Dipstick Microalbustix (visual) (Bayer)	Number of samples: 1 Early morning sample before the final 24-hour specimen was added to the 24-hour collection, a mixed 10-mL aliquot was removed for urinalysis.	NA Two semiquantitative immunoassays for albumin and Cr	Two observers	On waking, the first void was discarded and the sample started with the second urine specimen; the final specimen was the first void the following day.	NR Benzethonium chloride assay	NR
	DCA 2000 POC test (Bayer)	Number of samples: 1 Early morning sample before the final 24-hour specimen was added to the 24-hour collection, a mixed 10-mL aliquot was removed for urinalysis. Utilizes a cartridge system and 40 µL of sample.	NR Immunoturbidometric assay (albumin), colorimetric assay (Cr)	NR	On waking, the first void was discarded and the sample started with the second urine specimen; the final specimen was the first void the following day.	NR Benzethonium chloride assay	NR

Table 6. Index Tests and Reference Standard Characteristics of Included Diagnostic Accuracy Studies (Key Question 4a)

Study, Quality	Index Test (Make, Manufacturer)	Index Test Sampling Methods	Index Test Machine and Assay	Index Test Operator and Reader	24-Hour Ref Stand Collection Method	Ref Stand Machine and Assay	Ref Stand Operator and Reader
Kyle, 2008 ¹⁰⁶ Fair	Albumin:Cr spot test (DCA 2000, Bayer Healthcare LLC)	Number of samples: 1 Aliquot from midstream urine specimen before 24-hour; performed at antenatal clinic	NR NR	Research midwife	24-hour urine collection as an outpatient. Discard first void into the toilet and write date/time of the sample on the request form, all subsequent voids were collected. Final void collected 24 hours later and placed in specimen container.	NR Benzethonium chloride assay	NR
Index Test, Protein Dipstick							
Waugh, 2001 ¹¹² Fair	Dipstick (BM-Test 5L, Boehringer Mannheim UK)	Number of samples: 2 Two 10-mL aliquots of thoroughly mixed urine from the 24-hour urine; removed for dipstick analysis and protein assays.	NR NR	Observer	Collections performed between 8 am and 8 am on consecutive days; women instructed regarding collection procedures.	ExcelGel with silver staining kit Benzethonium chloride or Bradford assay	NR
Kyle, 2008 ¹⁰⁶ Fair	Dipstick (NR)	Number of samples: 1 Aliquot from midstream urine specimen before 24-hour	NR NR	Research midwife	24-hour urine collection as an outpatient. Discard first void into the toilet and write date/time of the sample on the request form, all subsequent voids were collected. Final void collected 24 hours later and placed in specimen container.	NR Benzethonium chloride assay	NR

Table 6. Index Tests and Reference Standard Characteristics of Included Diagnostic Accuracy Studies (Key Question 4a)

Study, Quality	Index Test (Make, Manufacturer)	Index Test Sampling Methods	Index Test Machine and Assay	Index Test Operator and Reader	24-Hour Ref Stand Collection Method	Ref Stand Machine and Assay	Ref Stand Operator and Reader
Waugh, 2005 ⁹⁴ Good	Dipstick Multistix 8SG (visual) (Bayer)	Number of samples: 1 Early morning sample before the final 24-hour specimen was added to the 24-hour collection, a mixed 10-mL aliquot was removed for urinalysis.	NA NA	Two observers	On waking, the first void was discarded and the sample started with the second urine specimen; the final specimen was the first void the following day.	NR Benzethonium chloride assay	NR
	Dipstick Multistix 8SG (automated) (Bayer)	Number of samples: 1 Early morning sample before the final 24-hour specimen was added to the 24-hour collection, a mixed 10-mL aliquot was removed for urinalysis.	Clinitek 50 NR	NR	On waking, the first void was discarded and the sample started with the second urine specimen; the final specimen was the first void the following day.	NR Benzethonium chloride assay	NR
Dwyer, 2008 ¹⁰⁵ Good	P/Cr automated dipstick (Iris test strips, IRIS Inc or Arcray Inc)	Number of samples: 1 Urinalysis; obtained before 24-hour collection, if a sample unavailable, taken immediately after 24-hour. All samples collected via clean catch unless the membranes had been ruptured, in which case specimens were captured by catheter.	Autoanalyzers 3'3"5'5" tetrachlorophenol -3,4,5,6-tetrabromo-sulfophthalein (protein error of pH indicator)	Laboratory technician	Most collected as outpatients, all samples collected via clean catch unless the membranes had been ruptured, in which case specimens were captured by catheter.	NR NR	Laboratory technician

Abbreviations: Cr=creatinine; NR=not reported; P=protein; ref=reference; stand=standard.

Table 7. Overall Summary of Evidence by Key Question

Key Question	No. of Studies (k), No. of Observations (n), Design	Quality	Limitations*	Consistency	U.S. Primary Care Applicability	Summary of Findings [†]
KQ1	0	NA	NA	NA	NA	NA
KQ1a Preeclampsia screening effects on health outcomes	k=1 n=2,764 RCT	Fair	Differences in the number of visits between the control and intervention groups were not as pronounced as intended by the design (12.0 vs. 14.7 visits). Insufficient power to detect differences in rare adverse outcomes such as very low birth weight, eclampsia, and stillbirth.	NA	Low Low-risk women seeking prenatal care in the first trimester in a large U.S. health maintenance organization. Study published nearly 20 years ago; there have been changes to clinical practice; insured women presenting for prenatal care in the first trimester of pregnancy may differ from those presenting at later gestations.	Fewer prenatal care visits did not have a beneficial or harmful effect on rates of health outcomes or diagnoses of preeclampsia, but evidence has limited relevance to current clinical practice or population.
KQ2 Preeclampsia multivariable risk assessment	k=4 external validation studies 16 externally validated risk assessment models 5 externally validated models with good to excellent discrimination (c-statistic ≥ 0.80) n=541–3,066 Prospective cohort	External validation in prospective cohort studies addresses common sources of bias in model development, we therefore included all externally validated risk prediction models in our review [†]	Calibration was not reported for any of the models, and risk cutpoints were not established a priori Many prediction models were developed by the same team of investigators, and the Australian cohort external validation studies were not independent from that group	Moderate/low Only one of the models was validated in more than one population, with similarly low positive predictive value, but inconsistently reported discrimination and detection.	Moderate The validation of some of the models in a diverse cohort of U.S. women with singleton pregnancies seeking routine prenatal care would be potentially applicable, but the impact of the model in other settings and in clinical use has not been evaluated.	No externally validated model was supported by evidence of good performance or clinical benefits Important model performance statistics were not available. Positive predictive values were low.

Table 7. Overall Summary of Evidence by Key Question

Key Question	No. of Studies (k), No. of Observations (n), Design	Quality	Limitations*	Consistency	U.S. Primary Care Applicability	Summary of Findings [†]
KQ3 Harms of preeclampsia multivariable risk assessment	k=1 n=255 Prospective cohort study	Fair	The risk assessment tool used was not clearly described, risk assessment occurred alongside intensive counseling and changes to clinical care and was not clearly described—cannot disentangle effects of risk assessment and clinical care Insufficient power to assess differences in effects of risk assessment for false-negative results compared with others.	NA	Low Study was conducted in Spain and Italy among women undergoing aneuploidy screening The risk assessment tool is unlikely to be used in practice based on external validation in U.S. cohort. ⁹⁹ Specially trained midwives conducted the risk assessment counseling visit.	Anxiety was not different between women screened as low and high risk for preeclampsia, but study groups were not equivalent. Comparisons in anxiety levels for women screened false negative could not be ascertained due to the timing of outcome measurement and insufficient power.
KQ4 Effectiveness of screening tests in identifying women with preeclampsia	0	NA	NA	NA	NA	NA

Table 7. Overall Summary of Evidence by Key Question

Key Question	No. of Studies (k), No. of Observations (n), Design	Quality	Limitations*	Consistency	U.S. Primary Care Applicability	Summary of Findings [†]
KQ4a Diagnostic accuracy of urine tests for proteinuria	k=14 n=1,888 Diagnostic accuracy studies	Fair	Spectrum bias was high as studies were limited to those with suspected preeclampsia (e.g., de novo hypertension, $\geq 1+$ dipstick) and not a broad range of pregnant women in primary care. High heterogeneity across studies; limited descriptions of tests and collection methods. Too few studies evaluating the diagnostic accuracy of dipsticks and albumin:creatinine spot urine tests to combine.	Moderate/Low Studies of protein:creatinine and albumin:creatinine spot urine tests had similar sensitivity and specificity, dipstick did not.	Moderate Six studies conducted in the United States; the remaining were conducted in European or South American countries with representative samples of pregnant women. All were conducted in women with suspected preeclampsia.	Protein:creatinine tests (k=12) had most evidence on test accuracy; sensitivity ranged from 0.65 to 0.96 and specificity from 0.49 to 1.00. Evidence of spectrum bias and high heterogeneity limit conclusions that can be drawn about test performance in routine clinical care. Dipstick urine tests least accurate (k=4). Sensitivity ranged from 0.22 to 1.00 and specificity from 0.36 to 1.00. Albumin:creatinine spot urine tests (k=2); sensitivity (0.94 and 1.00) and specificity (0.94 and 0.68).
KQ4b Effectiveness of different screening tests in identifying women with preeclampsia	0	NA	NA	NA	NA	No studies comparing the performance of different approaches to routine preeclampsia screening were identified. Within study comparisons from individual studies included for KQ4a provided limited evidence that: automated readings may be more accurate than visual; urine samples taken at different times of day have similar performance for the Albustix protein:creatinine test; and different assays used for evaluating 24-hour protein gold-standard give different results for test sensitivity.

Table 7. Overall Summary of Evidence by Key Question

Key Question	No. of Studies (k), No. of Observations (n), Design	Quality	Limitations*	Consistency	U.S. Primary Care Applicability	Summary of Findings†
KQ4c Effectiveness of different screening tests in identifying women at high or low risk for preeclampsia	0	NA	NA	NA	NA	NA
KQ5 Harms of preeclampsia screening	k=2 1 RCT n=2,764 1 before-after study n=1,952	Fair	Insufficient power to detect differences in rare adverse outcomes, such as very low birth weight and stillbirth RCT powered to detect differences of 2% or more between groups, but 1% differences for some outcomes could be clinically important Before-after study found a statistical difference in the source of payment for care over the study period, suggesting secular changes over time	NA Only 2 studies, similar finding that reductions in routine preeclampsia screening did not increase adverse maternal and infant health outcomes.	Moderate The RCT was published nearly 20 years ago, and there have been changes to clinical practices in the U.S., where the original study was conducted. The before-after study was among primarily underserved and race/ethnic minority patients obtaining care in a hospital-based midwifery practice in the U.S.	No differences in maternal, delivery or perinatal/ neonatal health outcomes when fewer preeclampsia screening visits during pregnancy ⁹⁷ or when urine testing conducted only when indicated (vs. routine urine screening). ¹¹⁵ Limitations in the timeliness of the research ⁹⁷ and weakness in study design ¹¹⁵ do not allow for strong conclusions about potential harms of different screening approaches to be made.

*Includes reporting bias.

†Includes precision.

‡ See methods for full explanation of the prediction model appraisal approach.

Abbreviations: KQ=key question; NA=not available; RCT=randomized, controlled trial.

Appendix A. Evidence on Preeclampsia Interventions to Reduce Morbidity and Mortality

Induction of labor/early delivery. Upon delivery, blood pressure and laboratory readings generally return to normal range values within a few days, although some women experience persistent high blood pressure that usually resolves within six weeks.¹⁷⁴ While delivery of the placenta is the only definitive treatment for preeclampsia, there are potential disadvantages including increased risk of neonatal complications¹⁷⁵ and increased risk of caesarean section.¹⁷⁶ Clinical decisions are based on the balance between risks of expectant management versus the risks of immediate induction of labor.¹⁷⁷ In cases of severe preeclampsia before 34 weeks of gestation, the effect of early delivery on neonatal and maternal outcomes is uncertain, with the exception of a decrease in the proportion of small for gestational age infants.¹⁷⁸⁻¹⁸⁰ Between 34 and 37 weeks of gestation, little is known about the risks of continuing pregnancy versus immediate delivery in women with preeclampsia.^{181,182}

To date, the only published prospective trials of gestational hypertension management are the HYPITAT¹⁸³ and HYPITAT-II¹⁷⁷ trials, both large multicenter open-label randomized controlled trials (RCTs) from the Netherlands evaluating the induction of labor versus expectant monitoring of hypertensive disorders at specific times during pregnancy. The first HYPITAT study found that immediate delivery reduced the risk of composite adverse maternal outcomes for women with preeclampsia after 37 weeks (RR, 0.71 [95% CI, 0.59 to 0.86]; $p < 0.0001$), with no differences in rates of cesarean section or neonatal outcomes.¹⁸³ Although trial evidence for assessing differences in outcomes with expectant management versus induced delivery was limited,¹⁸⁴ recommendations generally favor^{1,51,143} induction of labor rather than continuing observation in women with preeclampsia at term (≥ 37 weeks) as it reduces the time the mother and fetus are at risk of injury from preeclampsia complications, such as eclampsia and placental abruption.¹⁸⁵

For pregnant women diagnosed with preeclampsia without severe features at less than 37 weeks, expectant management, monitoring for disease progression rather than immediate delivery, is recommended.^{1,47,51} The HYPITAT-II trial found that for pregnant women with nonsevere hypertensive disorders (systolic blood pressure less than 170 mm Hg or diastolic blood pressure less than 110 mm Hg) between 34 to 36 weeks gestation, immediate delivery may slightly reduce the small risk of adverse maternal outcomes, but significantly increase the risk of neonatal respiratory distress syndrome.¹⁷⁷ Recommendations for preeclampsia with severe features between 34 and 37 weeks gestation are varied. Both the Society of Obstetricians and Gynecologists of Canada (SOGC) and National Institute for Health and Care Excellence (NICE) recommend delivery for all women who have preeclampsia with severe hypertension after 34 weeks,^{47,143} while the World Health Organization (WHO) advises a policy of expectant management provided that uncontrolled maternal hypertension, maternal organ dysfunction or fetal distress are absent.⁵¹

Trial evidence on the health outcomes associated with delivery versus expectant management of severe preeclampsia occurring before 34 weeks is limited and inconclusive.¹⁸⁶

Magnesium sulfate. Magnesium sulfate ($MgSO_4$) has been routinely used for the prevention of eclampsia seizures since the middle of the 20th century.¹⁸⁷ The Magpie Trial (n=10,141), an important international randomized placebo-controlled trial of magnesium sulfate to prevent eclampsia, established clear evidence of a benefit for preventing eclampsia with magnesium

Appendix A. Evidence on Preeclampsia Interventions to Reduce Morbidity and Mortality

sulfate among women for whom there was clinical uncertainty as to whether it should be administered.⁴⁹ Pregnant women given magnesium sulfate (n=40) had a 58 percent lower risk of eclampsia (95% CI, 40 to 71) than those allocated placebo (n=96).⁴⁹ Maternal mortality was also lower in the treatment group, although there were few cases (n=11; 0.2%) and the difference was not statistically significant (RR, 0.55 [95% CI, 0.26 to 1.14]).⁴⁹ Placental abruption was significantly lower in the treatment group, and there was no evidence of short term or longer term (up to 2 years) harms to the mother or offspring from the treatment. Following the trial, clinical management protocols have unequivocally recommended treatment of women with worsening or severe manifestations of preeclampsia to receive magnesium sulfate during delivery. A followup study of the Magpie Trial found that the use of magnesium sulfate in preeclamptic women demonstrated a 16 percent reduction in mortality and morbidity risk related to preeclampsia two to three years after delivery,¹⁸⁸ and no association with any difference in mortality and morbidity risk in children (18 months) whose mothers were recruited to the trial.¹⁸⁹ A recent Cochrane review of anticonvulsant management of preeclampsia found that magnesium sulfate more than halved the risk of eclampsia and likely reduced maternal death.¹⁸²

Guideline groups strongly agree on the importance of magnesium sulfate as first-line treatment of eclampsia as well as prophylaxis against eclampsia in women with severe preeclampsia.^{1,47,51,143}

Antihypertensive medications. Severe hypertension in pregnancy, regardless of the diagnosis of preeclampsia, poses a serious health risk to a pregnant woman and her fetus, and the use of antihypertensive medications is sometimes necessary to lower blood pressure to a safe range.^{190,191} Antihypertensive medications are used to prevent potential cardiovascular, renal, or cerebrovascular complications related to uncontrolled severe hypertension. The American Heart Association/American Stroke Association (AHA/ASA)⁴³ along with other professional guideline groups^{1,47,51,143} strongly recommend that women with severe hypertension during pregnancy be treated with safe and effective antihypertensive medications. The benefit of antihypertensive therapy is highlighted by the results of a 2014 retrospective chart review of over 1.2 million women delivering in a U.S. hospital system.⁵⁷ The analysis found a significant reduction in deaths from preeclampsia (15 to 3; p=0.02) following implementation of an automatic protocol for antihypertensive treatment during pregnancy.⁵⁷ There is not consensus, however, regarding the management of nonsevere hypertension.¹⁹¹ A recent Cochrane review of 49 trials assessed the effects of antihypertensive drug treatments for pregnant women with mild to moderate hypertension and found no statistically significant difference in preeclampsia risk, and no evidence of benefit or harm to the fetus.¹⁹²

Literature Search Strategies – Systematic Reviews

Database: Ovid MEDLINE(R) without Revisions <1996 to November Week 2 2013>, Ovid MEDLINE(R) Daily Update <November 20, 2013>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <November 20, 2013>

Search Strategy:

-
- 1 Pre-Eclampsia/ ()
 - 2 Hypertension, Pregnancy-Induced/ ()
 - 3 Eclampsia/ ()
 - 4 Pregnancy/ ()
 - 5 Hypertension/ ()
 - 6 4 and 5 ()
 - 7 1 or 2 or 3 or 6 ()
 - 8 Mass screening/ ()
 - 9 Biological markers/ ()
 - 10 Ultrasonography, Doppler/ ()
 - 11 "Predictive Value of Tests"/ ()
 - 12 "Sensitivity and Specificity"/ ()
 - 13 Diagnostic errors/ ()
 - 14 Risk factors/ ()
 - 15 Risk assessment/ ()
 - 16 (screen\$ or diagnos\$ or predict\$ or detect\$ or risk\$).ti. ()
 - 17 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 ()
 - 18 7 and 17 ()
 - 19 Pre-Eclampsia/di ()
 - 20 Hypertension, Pregnancy-Induced/di ()
 - 21 Eclampsia/di ()
 - 22 18 or 19 or 20 or 21 ()
 - 23 preeclamp\$.ti,ab. ()
 - 24 eclamp\$.ti,ab. ()
 - 25 gestosis.ti,ab. ()
 - 26 ((gestational or pregnan\$) adj5 (tox?emi\$ or hypertens\$)).ti,ab. ()
 - 27 23 or 24 or 25 or 26 ()
 - 28 (screen\$ or diagnos\$ or predict\$ or detect\$ or risk\$).ti,ab. ()
 - 29 27 and 28 ()
 - 30 limit 29 to ("in data review" or in process or "pubmed not medline") ()
 - 31 22 or 30 ()
 - 32 limit 31 to systematic reviews ()
 - 33 limit 32 to (english language and yr="2009 -Current") ()
 - 34 remove duplicates from 33 ()

Literature Search Strategies – Primary Literature

MEDLINE

Database: Ovid MEDLINE(R) <1946 to March Week 4 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <April 2, 2015>, Ovid MEDLINE(R) Daily Update <April 2, 2015>

Search Strategy:

-
- 1 Pre-Eclampsia/ ()
 - 2 Hypertension, Pregnancy-Induced/ ()
 - 3 Eclampsia/ ()
 - 4 Pregnancy/ ()
 - 5 Pregnancy Trimester, First/ ()
 - 6 Pregnancy Trimester, Second/ ()
 - 7 Pregnancy Trimester, Third/ ()
 - 8 Hypertension/ ()
 - 9 (4 or 5 or 6 or 7) and 8 ()
 - 10 (preeclamp\$ or pre eclamp\$.ti. ()
 - 11 eclamp\$.ti. ()
 - 12 gestosis.ti. ()
 - 13 ((gestational or pregnan\$) and (tox?emi\$ or hypertens\$ or blood pressure)).ti. ()
 - 14 1 or 2 or 3 or 9 or 10 or 11 or 12 or 13 ()
 - 15 Blood pressure/ ()
 - 16 Blood pressure determination/ ()
 - 17 Blood pressure monitoring, Ambulatory/ ()
 - 18 Blood pressure monitors/ ()
 - 19 Urinalysis/ ()
 - 20 Uric acid/ ()
 - 21 Proteinuria/ ()
 - 22 Pregnancy Proteins/ ()
 - 23 Uterine Artery/us ()
 - 24 Ultrasonography, Doppler/ ()
 - 25 Creatinine/ur ()
 - 26 Biological Markers/ ()
 - 27 Pregnancy-Associated Plasma Protein-A/ ()
 - 28 ((blood or systolic or diastolic) adj pressure).ti,ab. ()
 - 29 urinalys\$.ti,ab. ()
 - 30 (urine adj (measur\$ or analy\$ or test\$ or collect\$)).ti,ab. ()
 - 31 uric acid.ti,ab. ()
 - 32 (proteinuria or albuminuria or urine albumin).ti,ab. ()
 - 33 (ultrasound or ultrasonography).ti,ab. ()
 - 34 uterine artery doppler.ti,ab. ()
 - 35 ((biological or serum) adj3 (marker\$ or biomarker\$)).ti,ab. ()
 - 36 plasma protein a.ti,ab. ()
 - 37 or/15-36 ()
 - 38 Mass screening/ ()

Appendix B. Detailed Methods

- 39 screen\$.ti,ab. ()
- 40 (detect\$ or predict\$ or identif\$).ti. ()
- 41 38 or 39 or 40 ()
- 42 14 and (37 or 41) ()
- 43 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/ ()
- 44 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt. ()
- 45 Random\$.ti,ab. ()
- 46 control groups/ or double-blind method/ or single-blind method/ ()
- 47 clinical trial\$.ti,ab. ()
- 48 controlled trial\$.ti,ab. ()
- 49 meta analy\$.ti,ab. ()
- 50 epidemiologic studies/ or cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ ()
- 51 cohort\$.ti,ab. ()
- 52 longitudinal.ti,ab. ()
- 53 incidence stud\$.ti,ab. ()
- 54 retrospective.ti,ab. ()
- 55 (follow-up or followup).ti,ab. ()
- 56 prospective.ti,ab. ()
- 57 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 ()
- 58 42 and 57 ()
- 59 limit 58 to (english language and yr="1990 -Current") ()
- 60 remove duplicates from 59 ()
- 61 Risk/ ()
- 62 Risk factors/ ()
- 63 Risk assessment/ ()
- 64 risk\$.ti,ab. ()
- 65 multivariable prediction.ti,ab. ()
- 66 61 or 62 or 63 or 64 or 65 ()
- 67 14 and 66 ()
- 68 limit 67 to (english language and yr="1990 -Current") ()
- 69 remove duplicates from 68 ()
- 70 "Sensitivity and Specificity"/ ()
- 71 "Predictive Value of Tests"/ ()
- 72 ROC Curve/ ()
- 73 False Negative Reactions/ ()
- 74 False Positive Reactions/ ()
- 75 Diagnostic Errors/ ()
- 76 "Reproducibility of Results"/ ()
- 77 Reference Values/ ()
- 78 Reference Standards/ ()
- 79 Observer Variation/ ()
- 80 Receiver operat\$.ti,ab. ()
- 81 ROC curve\$.ti,ab. ()

Appendix B. Detailed Methods

- 82 sensitivit\$.ti,ab. ()
- 83 specificit\$.ti,ab. ()
- 84 predictive value.ti,ab. ()
- 85 accuracy.ti,ab. ()
- 86 false positive\$.ti,ab. ()
- 87 false negative\$.ti,ab. ()
- 88 miss rate\$.ti,ab. ()
- 89 error rate\$.ti,ab. ()
- 90 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85
or 86 or 87 or 88 or 89 ()
- 91 42 and 90 ()
- 92 limit 91 to (english language and yr="1990 -Current") ()
- 93 remove duplicates from 92 ()
- 94 Mortality/ ()
- 95 Morbidity/ ()
- 96 Death/ ()
- 97 safety.ti,ab. ()
- 98 harm\$.ti,ab. ()
- 99 mortality.ti,ab. ()
- 100 complication\$.ti,ab. ()
- 101 (death or deaths).ti,ab. ()
- 102 ((adverse or unintended or negative) adj (effect\$ or event\$ or reaction\$ or
outcome\$)).ti,ab. ()
- 103 (adverse effects or mortality).fs. ()
- 104 Cesarean Section/ ()
- 105 Magnesium Sulfate/to ()
- 106 Anxiety/ ()
- 107 Stress, Psychological/ ()
- 108 Premature Birth/ ()
- 109 (cesarean\$ or c-section\$).ti,ab. ()
- 110 hypermagnese\$.ti,ab. ()
- 111 (anxiety or anxious).ti,ab. ()
- 112 ((psychological or psychosocial or mental) adj (stress or distress or outcome\$)).ti,ab. ()
- 113 ((preterm or premature\$) adj (birth\$ or deliver\$)).ti,ab. ()
- 114 misdiagnos\$.ti,ab. ()
- 115 overdiagnos\$.ti,ab. ()
- 116 misclassification\$.ti,ab. ()
- 117 ((unnecessary or unneeded) adj3 (treat\$ or induc\$ or monitor\$)).ti,ab. ()
- 118 (increase\$ adj3 monitor\$).ti,ab. ()
- 119 or/94-118 ()
- 120 42 and 119 ()
- 121 limit 120 to (english language and yr="1990 -Current") ()
- 122 remove duplicates from 121 ()
- 123 60 or 69 or 93 or 122 ()
- 124 Animal/ not (Animal/ and Human/) ()
- 125 123 not 124 ()

Appendix B. Detailed Methods

PubMed

Query

Search (((#24) AND publisher[sb]) AND English[Language]) AND ("1990"[Date - Publication]: "3000"[Date - Publication])

Search (#10 AND #23)

Search #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22

Search "multivariable prediction"[tiab]

Search risk*[tiab]

Search "plasma protein a"[tiab]

Search biological marker*[tiab] OR biological biomarker*[tiab] OR serum marker*[tiab] OR serum biomarker*[tiab]

Search "uterine artery doppler"[tiab]

Search (ultrasound[tiab] or ultrasonography[tiab])

Search (proteinuria[tiab] or albuminuria[tiab] or "urine albumin"[tiab])

Search urine[tiab] AND (measur*[tiab] OR analy*[tiab] OR test*[tiab] OR collect*[tiab])

Search urinalys*[tiab]

Search blood pressure[tiab] OR systolic pressure[tiab] OR diastolic pressure[tiab]

Search (detect*[title] OR predict*[title] OR identif*[title])

Search screen*[tiab]

Search (#8 OR #9)

Search (hypertens*[title] OR blood pressure[title] OR toxemi*[title] OR toxaemi*[title]) AND (gestational[title] OR pregnan*[title])

Search pre eclampsia[title] OR preeclampsia[title] OR pre eclamptic[title] OR preeclamptic[title] or eclampsia[title] or eclamptic[title] or gestosis[title])

Cochrane Central Register of Controlled Clinical Trials (CENTRAL)

#1 preeclamp*:ti,ab,kw

#2 (pre-eclampsia or pre-eclamptic):ti,ab,kw

#3 eclamp*:ti,ab,kw

#4 gestosis:ti,ab,kw

#5 #1 or #2 or #3 or #4

#6 hypertension:ti,ab,kw

#7 hypertensive:ti,ab,kw

#8 (toxemi*:ti,ab,kw or toxaemi*:ti,ab,kw)

#9 "blood pressure":ti,ab,kw near/5 (high or elevated or abnormal):ti,ab,kw

#10 #6 or #7 or #8 or #9

#11 "pregnancy":ti,ab,kw

#12 "pregnant":ti,ab,kw

#13 gestational:ti,ab,kw

#14 #11 or #12 or #13

#15 #10 and #14

#16 #5 or #15

#17 screen*:ti,ab,kw

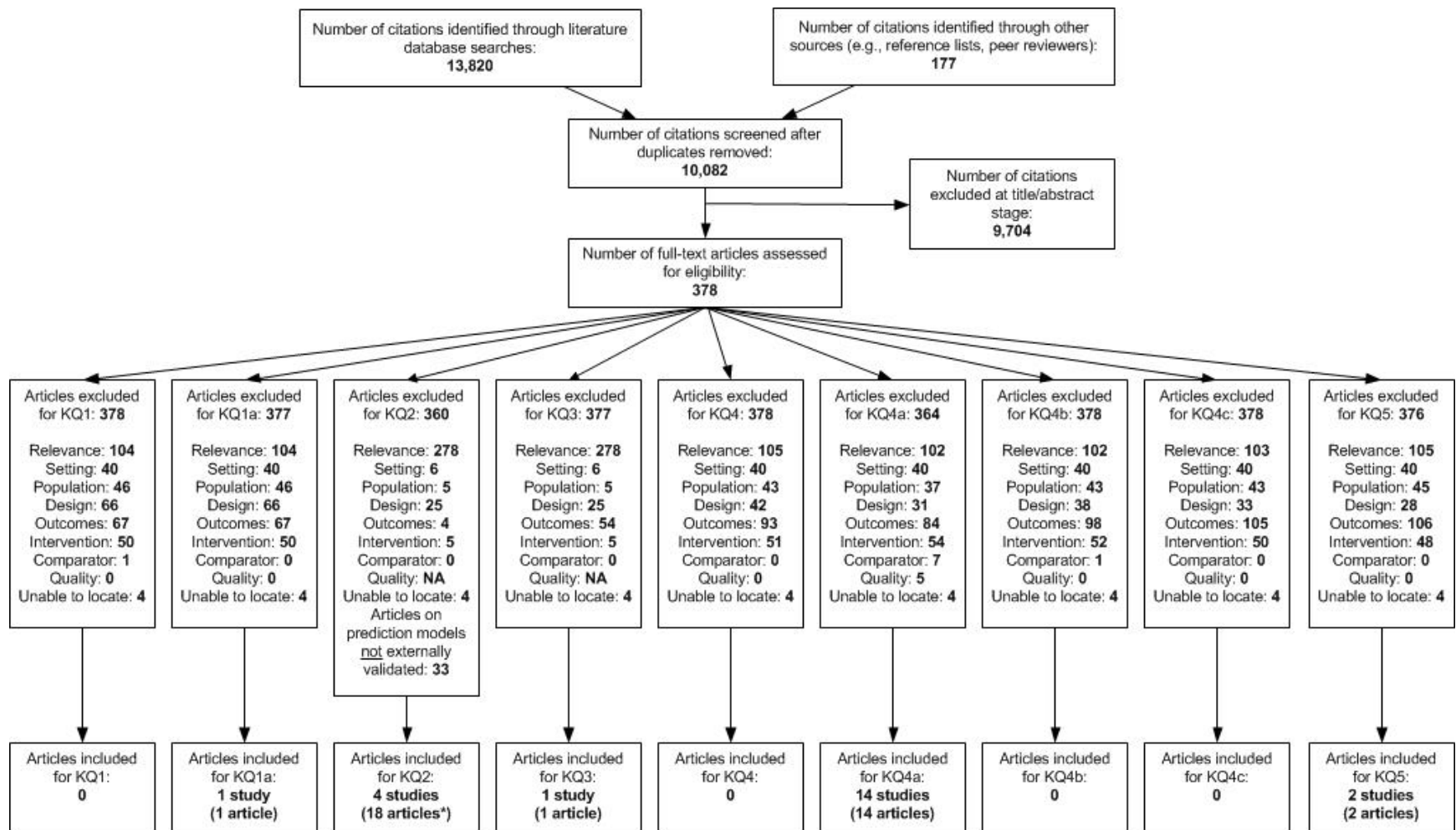
#18 (detect* or predict* or identif*):ti

#19 (blood or systolic or diastolic):ti,ab,kw next pressure:ti,ab,kw

Appendix B. Detailed Methods

- #20 urinalys*:ti,ab,kw
- #21 urine:ti,ab,kw next (measur* or analy* or test* or collect*):ti,ab,kw
- #22 (proteinuria or albuminuria or "urine albumin"):ti,ab,kw
- #23 (ultrasound or ultrasonography):ti,ab,kw
- #24 "uterine artery doppler":ti,ab,kw
- #25 (biological or serum):ti,ab,kw near/3 (marker* or biomarker*):ti,ab,kw
- #26 "plasma protein a":ti,ab,kw
- #27 risk*:ti,ab,kw
- #28 "multivariable prediction":ti,ab,kw
- #29 #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28
- #30 #16 and #29 Publication Year from 1990 to 2014, in Trials

Appendix B Figure 1. Literature Flow Diagram



* We included four studies (7 articles) on externally validated risk prediction models. We also identified 11 articles that represent the model development studies related to the external validation studies.

Abbreviations: KQ=key question.

Appendix B Table 1. Inclusion and Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
Populations	All pregnant women without a diagnosis of preeclampsia and asymptomatic for preeclampsia including pregnant women with common chronic conditions seen in primary care (i.e., hypertension, diabetes mellitus) and at elevated risk for preeclampsia	Studies that exclusively include individuals seeking high-risk obstetric care (e.g., in-vitro fertilization); inpatients or hospitalized; other selected non-generalizable populations or populations with other preexisting health conditions (e.g., HIV, HPV, hepatitis, autoimmune disorders, polycystic ovarian syndrome, renal disease, organ transplant recipients, sickle cell trait)
Disease/ Condition	KQ1, 1a: Eclampsia, maternal morbidity and mortality, perinatal/neonatal morbidity and mortality KQ2, KQ4: Preeclampsia KQ3, KQ5: Eclampsia, maternal morbidity and mortality (including psychological effects of risk assessment and screening), perinatal/neonatal morbidity and mortality	
Interventions: Preeclampsia Risk Assessment and Screening	KQs 1, 4, 5: Screening occurs from 20 weeks gestation to delivery. Screening tests for preeclampsia are blood pressure measurement and urine protein tests KQ4a: Point of care urine tests (e.g., dipstick or random urine spot test) KQs 2, 3: Risk assessment occurring before 20 weeks gestation using multivariable prediction tools for the identification of women at high risk for preeclampsia	Experimental tests that are not routinely used for preeclampsia screening in clinical practice Secondary evaluations and tests used to assess preeclampsia severity or confirm diagnosis in symptomatic women Urine screening tests requiring ongoing collection of urine 24 hour ambulatory blood pressure measurements Risk assessment occurring after 20 weeks gestation Non-routine screening tests: Serum markers (e.g., angiogenic factors, activated protein C, calcium, HCG, HcY, hormones, lipids, thyroid hormone levels) Genetic susceptibility markers (e.g., fetal DNA) Ultrasound measurements (e.g., Doppler ultrasound pulsatility index or resistance index; pulse wave velocity or notching)
Comparisons	KQ 1: No screening, different screening protocols (e.g., modality, timing, rescreen interval) KQ3: Usual care; low risk KQs 4, 5: Different blood pressure and proteinuria screening protocols (e.g., instrument, procedure, timing, frequency) and screening protocols KQ4a: Reference standard is 24 hour urine collection (for proteinuria)	Reference standard other than 24 hour urine collection for protein measurement

Appendix B Table 1. Inclusion and Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
Outcomes	<p>KQ1 (maternal and perinatal health outcomes): Maternal mortality and serious morbidity (e.g., organ or system failure or injury, eclampsia) and perinatal or neonatal mortality and serious morbidity (e.g., intrauterine growth restriction, low birth weight, brain injury)</p> <p>KQs 2 (intermediate outcome): Prediction, discrimination, calibration outcomes for preeclampsia risk prediction model (e.g., AUC, Brier score)</p> <p>KQ 4 (intermediate outcomes): Test performance characteristics, sensitivity, specificity, for accuracy and effectiveness of screening.</p> <p>KQs 3, 5 (harms): Misclassification, increased monitoring, false positives, overdiagnosis, overtreatment (e.g., failed induction, Cesarean section, induced preterm birth, hypermagnesemia), and patient stress and anxiety</p>	<p>Nonclinical health outcomes, such as length of hospital stay (without indication), intensive care unit admission, or neonatal intensive care unit admission.</p> <p>KQ 4: Bivariable or multivariable regression (e.g., correlations)</p>
Setting	<p>Primary care outpatient settings for obstetric care (e.g., obstetrician gynecologists, family physicians, certified nurse midwives)</p> <p>Countries categorized as “Very High” or equivalent on the Human Development Index (as defined by the World Health Organization, 2014)</p>	<p>Clinics and study sites treating only high risk maternity patients</p> <p>Countries not categorized as “Very High” on the Human Development Index or not applicable to U.S. clinical settings or populations</p>
Study Designs	<p>KQ1: RCTs</p> <p>KQ2: Nested case-control or cohort study aiming to externally validate a multivariable clinical risk prediction tool; randomized impact studies comparing clinical risk prediction based care to usual care</p> <p>KQ4: RCTs, cohort studies, instrument validation studies, and test accuracy studies</p> <p>KQs 3, 5: RCTs or observational studies (e.g., nested case control, case series, cohort, registry, survey data)</p>	<p>KQ1: Case-control study, editorial, narrative review, commentary, postmarketing surveillance, and case report.</p> <p>KQ4: Case-control study, editorial, narrative review, commentary, postmarketing surveillance, and case reports</p> <p>KQs 3, 5: Editorial, narrative review, commentary, postmarketing surveillance, and case reports</p>
Publication Dates	<p>Studies published after January 1990, all references from the previous USPSTF review, and eligible studies identified through a bridge search</p>	<p>Studies published before 1990</p>
Study Quality	<p>Good and fair quality according to USPSTF design-specific criteria</p>	<p>Poor quality according to USPSTF design-specific criteria</p>
Language	<p>English</p>	<p>Non-English studies</p>

*Settings: Included Countries: All countries listed as “very high” or equivalent on human development on the Human Development Index, 2014 (<http://hdr.undp.org/en/statistics/>): Andorra, Argentina, Australia, Austria, Barbados, Belgium, Brunei Darussalam, Canada, Chile, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, New Zealand, Norway, Poland, Portugal, Qatar, Seychelles, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, Taiwan, United Arab Emirates, United Kingdom, United States

Abbreviations: RCT= randomized, controlled trial.

Appendix B Table 2. Quality Assessment Criteria

Study Design	Adapted Quality Criteria
Randomized controlled trials, adapted from the U.S. Preventive Services Task Force methods ⁸⁷	Was there valid random assignment? Was allocation concealed? Was eligibility criteria specified? Were groups similar at baseline? Were the outcome assessors blinded? Was there intervention fidelity? Was there adequate adherence to the intervention? Were measurements equal, valid and reliable? Was there acceptable followup? Was there a difference between those who completed the study and those who withdrew? Was the handling of missing data appropriate? Were the statistical methods acceptable? Was there evidence of selective reporting of outcomes?
Observational studies (e.g., prospective cohort studies), adapted from the Newcastle-Ottawa Scale (NOS) ⁸⁹	Was there representativeness of the exposed cohort? Was the non-exposed systematically selected? Was the ascertainment of exposure reported? Was eligibility criteria specified? Comparability of cohorts on the basis of design or analysis? Was the outcome of interest not present at baseline? Were measurements equal, valid and reliable? Were outcome assessors blinded? Was followup long enough for the outcome to occur? Was there adequate followup of cohorts? Was there adjustment for confounders? Were the statistical methods acceptable? Was the handling of missing data appropriate?
Diagnostic accuracy studies, adapted from the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) II instrument ⁸⁸	Could the selection of patients have introduced bias? Was a consecutive or random sample of patients enrolled? Was a case-control design avoided? Did the study avoid inappropriate exclusions? Could the conduct or interpretation of the index test have introduced bias? Was the index test interpreted without knowledge of the reference standard results? If a threshold was used, was it pre-specified? Was the fidelity of the index test monitored and/or reported? Could the conduct or interpretation of the reference standard have introduced bias? Was the reference standard interpreted without knowledge of the index test results? Was the fidelity of the reference test monitored and/or reported? Could the patient flow have introduced bias? Was there an appropriate interval between the index test and reference standard? Did all patients receive the same reference standard? Did all patients complete all tests? Were all patients completing both tests included in the analysis?
Before-After ⁸⁹	Is the post-intervention group representative? Is the pre-intervention group representative? Are the pre- and post-intervention groups comparable on the basis of design or analysis? Was the assessment of outcomes valid? Was the assessment of outcomes reliable? Was the method of outcome assessment the same for the pre- and post-intervention groups? Did the study report the point of time when the intervention occurred? Was the intervention clearly described? Were the data collected during a similar timeframe?

Appendix C. Preeclampsia Diagnostic Criteria Included in Major Guidelines and Recommendations, 1972–2013

Organization	Hypertension	Proteinuria	Other Diagnostic Indicators (Symptoms, Blood Test Results, or Health Outcomes)
United States			
American College of Obstetricians and Gynecologists (ACOG) 2013, U.S. ¹	<p><i>Preeclampsia <u>must</u> include 1 of the following:</i> SBP \geq140 mm Hg or DBP \geq90 mm Hg on 2 occasions >4 hours apart after 20 weeks' gestation in a previously normotensive woman If SBP \geq160 mm Hg or DBP \geq110 mm Hg, hypertension can be confirmed within a short interval to facilitate timely delivery of antihypertensive therapy</p> <p><i>Severe preeclampsia <u>may</u> include:</i> SBP \geq160 mm Hg or DBP \geq110 mm Hg on 2 occasions >4 hours apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time)</p>	<p><i>Preeclampsia <u>may</u> include 1 of the following:</i> \geq300 mg protein per 24-hour urine collection Protein:creatinine ratio \geq0.3 mg/dL Dipstick reading of 1+ (used only if other quantitative methods not available)</p> <p><i>Severe preeclampsia <u>may</u> include:</i> Serum creatinine concentration >1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease</p>	<p><i>In the absence of proteinuria, preeclampsia can be confirmed by new-onset hypertension and 1 of the following:</i> Thrombocytopenia Renal insufficiency Impaired liver function Pulmonary edema Cerebral or visual symptoms</p> <p><i>Severe preeclampsia <u>may</u> include:</i> Thrombocytopenia Progressive renal insufficiency Impaired liver function Pulmonary edema Cerebral or visual disturbances</p>
American College of Obstetricians and Gynecologists (ACOG) 2002, U.S. ⁷⁹ <i>Based on NHLBI Working Group 2000</i>	<p><i>Preeclampsia <u>must</u> include:</i> SBP \geq140 mm Hg or DBP \geq90 mm Hg presenting after 20 weeks' gestation in a previously normotensive woman</p> <p><i>Severe preeclampsia <u>may</u> include:</i> SBP \geq160 mm Hg or DBP \geq110 mm Hg on 2 occasions \geq6 hours apart while on bed rest</p>	<p><i>Preeclampsia <u>must</u> include:</i> \geq0.3 g protein per 24-hour urine collection (correlates with \geq1+ reading on dipstick but should be confirmed using a random urine evaluation)</p> <p><i>Severe preeclampsia <u>may</u> include:</i> \geq5 g protein per 24-hour urine collection or dipstick \geq3+ on 2 random urine samples collected \geq4 hours apart</p>	<p><i>Preeclampsia <u>may</u> include:</i> Edema Visual disturbances Headache Epigastric pain Hemolysis Elevated liver enzymes Low platelet counts (HELLP syndrome)</p> <p><i>Severe preeclampsia <u>may</u> include 1 of the following:</i> Oliguria of <500 mL in 24 hours Cerebral or visual disturbances Pulmonary edema or cyanosis Epigastric or right upper-quadrant pain Impaired liver function Thrombocytopenia Fetal growth restriction</p>

Appendix C. Preeclampsia Diagnostic Criteria Included in Major Guidelines and Recommendations, 1972–2013

Organization	Hypertension	Proteinuria	Other Diagnostic Indicators (Symptoms, Blood Test Results, or Health Outcomes)
<p>National Heart, Lung, and Blood Institute (NHLBI) Working Group 2000, U.S.¹⁹³</p> <p><i>Update of NHLBI Working Group 1990</i></p>	<p><i>Preeclampsia <u>must</u> include:</i> SBP >140 mm Hg or DBP >90 mm Hg presenting after 20 weeks' gestation in a previously normotensive woman</p>	<p><i>Preeclampsia <u>must</u> include:</i> ≥0.3 g protein per 24-hour urine collection (correlates with ≥30 mg/dL in a random urine determination or ≥1+ reading on dipstick)</p>	<p><i>In the <u>absence of proteinuria</u>, preeclampsia is highly suspected when hypertension appears with the following:</i> Headache Blurred vision Abdominal pain Low platelet counts Abnormal liver enzyme values</p> <p><i>Edema occurs in too many women with normal pregnancies and has been removed as a marker in the classification of preeclampsia</i></p>
<p>National Heart, Lung, and Blood Institute (NHLBI) Working Group 1990, U.S.¹⁹⁴</p> <p><i>Minimally updated from ACOG 1972</i></p>	<p><i>Preeclampsia <u>must</u> include 1 of the following:</i> SBP ≥140 mm Hg or DBP ≥90 mm Hg presenting after 20 weeks' gestation in a previously normotensive woman SBP increases of ≥30 mm Hg or DBP increases of ≥15 mm Hg from early values before 20 weeks' gestation</p>	<p><i>Preeclampsia <u>may</u> include:</i> ≥0.3 g protein per 24-hour urine collection (correlates with ≥30 mg/dL in a random urine determination or ≥1+ reading on dipstick)</p>	<p><i>Preeclampsia <u>may</u> include:</i> Edema</p>
United Kingdom			
<p>National Institute for Health and Care Excellence (NICE) 2010, U.K.⁴⁷</p> <p><i>Decision made on March 2015 that the guidelines should not be updated at this time</i></p>	<p><i>Preeclampsia <u>must</u> include:</i> SBP ≥140 mm Hg or DBP ≥90 mm Hg presenting after 20 weeks' gestation in a previously normotensive woman</p> <p><i>Severe preeclampsia <u>must</u> include 1 of the following:</i> SBP ≥160 mm Hg or DBP ≥110 mm Hg SBP ≥140 mm Hg or DBP ≥90 mm Hg (mild hypertension) or SBP ≥150 mm Hg or DBP ≥100 mm Hg (moderate hypertension) with other diagnostic indicators</p>	<p><i>Preeclampsia <u>must</u> include 1 of the following:</i> >300 mg protein per 24-hour urine collection Protein:creatinine ratio >30 mg/mmol</p> <p><i>Severe preeclampsia <u>must</u> include 1 of the following:</i> >300 mg protein per 24-hour urine collection Protein:creatinine ratio >30 mg/mmol</p>	<p><i>In the <u>absence of severe hypertension</u>, features of severe preeclampsia include mild/moderate hypertension <u>and</u> proteinuria with ≥1 of the following:</i> Severe headache Problems with vision such as blurring or flashing Severe pain just below ribs or vomiting Papilloedema Signs of clonus (≥3 beats) Liver tenderness HELLP syndrome Platelet count falls to <100 x 10⁹/L Abnormal liver enzymes</p>

Appendix C. Preeclampsia Diagnostic Criteria Included in Major Guidelines and Recommendations, 1972–2013

Organization	Hypertension	Proteinuria	Other Diagnostic Indicators (Symptoms, Blood Test Results, or Health Outcomes)
Canada			
Society of Obstetricians and Gynecologists of Canada (SOGC) 2014, Canada ¹⁴³	<p><i>Preeclampsia <u>must</u> include:</i> SBP ≥140 mm Hg or DBP ≥90 mm Hg (based on the average of ≥2 measurements taken ≥15 minutes apart) after 20 weeks' gestation in a previously normotensive woman</p>	<p><i>Preeclampsia <u>may</u> include 1 of the following:</i> ≥0.3 g protein per 24-hour urine collection ≥30 mg/mmol urinary creatinine in a spot (random) urine sample</p>	<p><i>In the <u>absence of proteinuria</u>, preeclampsia can be confirmed by new-onset hypertension <u>and</u> 1 of the following:</i> Adverse condition (headache, visual symptoms, chest pain, low platelet count, nausea or vomiting, epigastric pain) Severe complication (eclampsia, stroke, uncontrolled severe hypertension, platelet count <50 x 10⁹/L, acute kidney injury, hepatic dysfunction, abruption with evidence of maternal fetal compromise)</p>

Abbreviations: DBP=diastolic blood pressure; HELLP=hemolysis, elevated liver enzymes, low platelet count; SBP=systolic blood pressure.

Appendix D. Excluded Studies

Code	Reason for Exclusion
E1	Setting Clinics and study sites treating only high risk maternity patients Countries not categorized as “very high HDI” equivalent or not applicable to U.S. clinical settings
E2	Population Patients seeking high risk obstetric care or those with known chronic conditions (other than hypertension or diabetes) Hospitalized patients
E3	Study Design Editorial, narrative review, commentary, post-marketing surveillance, case reports Not approved study design for the KQ Risk factor screening occurred after 20 weeks gestation (KQ2) Case-control study (KQ4) Case-control study, but not nested (KQ1, KQ2) N too small (<100) (KQ2)
E4	Outcomes Non-clinical health outcomes, such as length of hospital stay (without indication), ICU admission, or NICU admission
E5	Disease/Condition Not preeclampsia or eclampsia (KQ1, KQ2) Not proteinuria (KQ4a) Not hypertension (KQ4b)
E6	Interventions Serum markers or ultrasound measurements not routinely collected Secondary evaluations or diagnostic tests Experimental tests Not a screening tool (e.g., prognostic assessment)
E7	Comparisons Comparators (e.g., not the appropriate reference standard)
E8	Language Non-English publication
E9	Publication Date Published before 1990
E10	Study Quality Poor
E11	Unable to locate article
E12	Study Aim Not applicable/relevant to key question
E13	Non-externally validated risk prediction models (KQ2)

1. Abebe J, Eigbefoh J, Isabu P, et al. Accuracy of urine dipsticks, 2-h and 12-h urine collections for protein measurement as compared with the 24-h collection. *J Obstet Gynaecol* 2008 Jul;28(5):496-500. PMID: 18850422. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
2. Abi-Said D, Annegers JF, Combs-Cantrell D, et al. Case-control study of the risk factors for eclampsia. *Am J Epidemiol* 1995 Aug 15;142(4):437-41. PMID: 7625409. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
3. Abou El HM, Diamandis EP, Karumanchi SA, et al. Preeclampsia: An Old Disease with New Tools for Better Diagnosis and Risk Management. *Clin Chem* 2015 Jan 22;61(5):694-8. PMID: 25614469. **KQ1E3, KQ1aE3, KQ2E3, KQ3E3, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
4. Adelberg AM, Miller J, Doerzbacher M, et al. Correlation of quantitative protein measurements in 8-, 12-, and 24-hour urine samples for the diagnosis of preeclampsia. *Am J Obstet Gynecol* 2001 Oct;185(4):804-7. PMID: 11641655. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**

Appendix D. Excluded Studies

5. Akaishi R, Yamada T, Morikawa M, et al. Clinical features of isolated gestational proteinuria progressing to pre-eclampsia: retrospective observational study. *BMJ Open* 2014;4(4):e004870. PMID: 24747797. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
6. Akolekar R, Syngelaki A, Sarquis R, et al. Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11-13 weeks. *Prenat Diagn* 2011 Jan;31(1):66-74. PMID: 21210481. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
7. Akolekar R, Syngelaki A, Poon L, et al. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. *Fetal Diagn Ther* 2013;33(1):8-15. PMID: 22906914. **KQ1E12, KQ1aE12, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
8. Al RA, Baykal C, Karacay O, et al. Random urine protein-creatinine ratio to predict proteinuria in new-onset mild hypertension in late pregnancy. *Obstet Gynecol* 2004 Aug;104(2):367-71. PMID: 15292013. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
9. Al RA, Borekci B, Yapca O, et al. Albumin/creatinine ratio for prediction of 24-hour albumin excretion of > or =2 g in manifest preeclampsia. *Clin Exp Obstet Gynecol* 2009;36(3):169-72. PMID: 19860361. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
10. Albers LL, Overman B, Sedler KD. Intrapartum hypertension in a low-risk obstetric population. *J Nurse Widwifery* 1998 Mar;43(2):106-10. PMID: 9581096. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
11. Alves E, Azevedo A, Rodrigues T, et al. Impact of risk factors on hypertensive disorders in pregnancy, in primiparae and multiparae. *Ann Hum Biol* 2013 Sep;40(5):377-84. PMID: 23682598. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
12. Amin SV, Illipilla S, Hebbar S, et al. Quantifying proteinuria in hypertensive disorders of pregnancy. *Int J Hypertens* 2014;2014:941408. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
13. Ananth CV, Vintzileos AM. Ischemic placental disease: epidemiology and risk factors. *Eur J Obstet Gynecol Reprod Biol* 2011 Nov;159(1):77-82. PMID: 21839575. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
14. Anderson UD, Gram M, Akerstrom B, et al. First trimester prediction of preeclampsia. *Current Hypertension Reports* 2015 Sep;17(9):584. PMID: 26232922. **KQ1E3, KQ1aE3, KQ2E3, KQ3E3, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
15. Anumba DO, Lincoln K, Robson SC. Predictive value of clinical and laboratory indices at first assessment in women referred with suspected gestational hypertension. *Hypertens Pregnancy* 2010 Jan;29(2):163-79. PMID: 20367506. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
16. Arfeen ZU, Maran NJ, Simon EJ, et al. A comparison of non-invasive methods of blood pressure measurement in normotensive and hypertensive pregnant women. *Int J Obstet Anesth* 1996 Jul;5(3):168-71. PMID: 15321344. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
17. August P, Helseth G, Cook EF, et al. A prediction model for superimposed preeclampsia in women with chronic hypertension during pregnancy. *Am J Obstet Gynecol* 2004 Nov;191(5):1666-72. PMID: 15547540. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
18. Ayala DE, Hermida RC, Mojon A, et al. Blood pressure variability during gestation in healthy and complicated pregnancies. *Hypertension* 1997 Sep;30(3:Pt 2):t-8. PMID: 9322990. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**

Appendix D. Excluded Studies

19. Bahado-Singh RO, Syngelaki A, Akolekar R, et al. Validation of metabolomic models for prediction of early-onset preeclampsia. *Am J Obstet Gynecol* 2015 Jun 23 PMID: 26116099. **KQ1E12, KQ1aE12, KQ2E6, KQ3E6, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
20. Bahasadri S, Kashanian M, Khosravi Z. Comparison of pregnancy outcome among nulliparas with and without microalbuminuria at the end of the second trimester. *Int J Gynaecol Obstet* 2011 Oct;115(1):34-6. PMID: 21794863. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
21. Baker PN, Hackett GA. The use of urinary albumin-creatinine ratios and calcium-creatinine ratios as screening tests for pregnancy-induced hypertension. *Obstet Gynecol* 1994 May;83(5:Pt 1):t-9. PMID: 8164937. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE6, KQ4bE4, KQ4cE4, KQ5E4.**
22. Bakker R, Steegers EA, Hofman A, et al. Blood pressure in different gestational trimesters, fetal growth, and the risk of adverse birth outcomes: the generation R study. *Am J Epidemiol* 2011 Oct 1;174(7):797-806. PMID: 21859836. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
23. Bar J, Hod M, Erman A, et al. Microalbuminuria as an early predictor of hypertensive complications in pregnant women at high risk. *Am J Kidney Dis* 1996 Aug;28(2):220-5. PMID: 8768917. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
24. Bar J, Friedman S, Erman A, et al. Microalbuminuria as an early marker of severity in hypertensive pregnant women. *J Hum Hypertens* 1996 Sep;10(Suppl 3):S111-S114. PMID: 8872840. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
25. Bar J, Maymon R, Padoa A, et al. White coat hypertension and pregnancy outcome. *J Hum Hypertens* 1999 Aug;13(8):541-5. PMID: 10455476. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
26. Barton JR, Barton LA, Istwan NB, et al. Elective delivery at 340(/)7 to 366(/)7 weeks' gestation and its impact on neonatal outcomes in women with stable mild gestational hypertension. *Am J Obstet Gynecol* 2011 Jan;204(1):44-5. PMID: 20934682. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
27. Baschat AA, Magder LS, Doyle LE, et al. Prediction of preeclampsia utilizing the first trimester screening examination. *Am J Obstet Gynecol* 2014 Apr 15;211(5):e1-e7. PMID: 24746997. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
28. Bateman BT, Bansil P, Hernandez-Diaz S, et al. Prevalence, trends, and outcomes of chronic hypertension: a nationwide sample of delivery admissions. *Am J Obstet Gynecol* 2012 Feb;206(2):134-8. PMID: 22177190. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
29. Baweja S, Kent A, Masterson R, et al. Prediction of pre-eclampsia in early pregnancy by estimating the spot urinary albumin: creatinine ratio using high-performance liquid chromatography. *BJOG* 2011 Aug;118(9):1126-32. PMID: 21481153. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E3, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
30. Becker R, Keller T, Kiesewetter H, et al. Individual risk assessment of adverse pregnancy outcome by multivariate regression analysis may serve as basis for drug intervention studies: retrospective analysis of 426 high-risk patients including ethical aspects. *Arch Gynecol Obstet* 2013 Jul;288(1):41-8. PMID: 23389246. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
31. Bellomo G, Rondoni F, Pastorelli G, et al. Twenty four-hour ambulatory blood pressure monitoring in women with pre-eclampsia. *J Hum Hypertens* 1995 Aug;9(8):617-21. PMID: 8523375. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**

Appendix D. Excluded Studies

32. Bellomo G, Narducci PL, Rondoni F, et al. Prognostic value of 24-hour blood pressure in pregnancy. *JAMA* 1999 Oct 20;282(15):1447-52. PMID: 10535435. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
33. Bener A, Saleh NM. The impact of socio-economic, lifestyle habits, and obesity in developing of pregnancy-induced hypertension in fast-growing country: global comparisons. *Clin Exp Obstet Gynecol* 2013;40(1):52-7. PMID: 23724507. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
34. Beunis MH, Schweitzer KJ, van Hooff MH, et al. Midtrimester screening for microalbuminuria in healthy pregnant women. *J Obstet Gynaecol* 2004 Nov;24(8):863-5. PMID: 16147637. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4aE7, KQ4bE4, KQ4cE4, KQ5E4.**
35. Bhide A, Rana R, Dhavilkar M, et al. The value of the urinary protein:creatinine ratio for the detection of significant proteinuria in women with suspected preeclampsia. *Acta Obstet Gynecol Scand* 2015 Mar 3;94(5):542-6. PMID: 25737188. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E4, KQ4bE4, KQ4cE4, KQ5E2.**
36. Binstock MA, Wolde-Tsadik G. Alternative prenatal care. Impact of reduced visit frequency, focused visits and continuity of care. *J Reprod Med* 1995 Jul;40(7):507-12. PMID: 7473439. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
37. Biswas A, Choolani MA, Anandakumar C, et al. Ambulatory blood pressure monitoring in pregnancy induced hypertension. *Acta Obstet Gynecol Scand* 1997 Oct;76(9):829-33. PMID: 9351407. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
38. Booker CJ, Dodson WC, Kunselman AR, et al. Twenty-four-hour ambulatory blood pressure monitor heart rate: a potential marker for gestational hypertension in at-risk women. *Am J Perinatol* 2012 May;29(5):339-46. PMID: 22147639. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
39. Boucoiran I, Thissier LS, Wu Y, et al. Risk for preeclampsia and intrauterine growth restriction: Effective value of PIGF, Sflt-1 and Inhibin A in singleton and multiple pregnancies. *Am J Obstet Gynecol* 2012;206:S336-S337. PMID: None. **KQ1E12, KQ1aE12, KQ2E6, KQ3E6, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
40. Bramham K, Poli-de-Figueiredo CE, Seed PT, et al. Association of proteinuria threshold in pre-eclampsia with maternal and perinatal outcomes: a nested case control cohort of high risk women. *PLoS One* 2013;8(10):e76083. PMID: 24130760. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
41. Broughton PF, Sharif J, Lal S. Predicting high blood pressure in pregnancy: a multivariate approach. *J Hypertens* 1998 Feb;16(2):221-9. PMID: 9535150. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
42. Brown MA, Buddle ML, Whitworth JA. Measurement of blood pressure during pregnancy: evaluation of the "TriCUFF". *Aust N Z J Obstet Gynaecol* 1993 Feb;33(1):48-50. PMID: 8498938. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
43. Brown MA, Buddle ML, Cario GM, et al. Ambulatory blood pressure monitoring during pregnancy. Comparison with mercury sphygmomanometry. *Am J Hypertens* 1993 Sep;6(9):745-9. PMID: 8110427. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
44. Brown MA, Wang MX, Buddle ML, et al. Albumin excretory rate in normal and hypertensive pregnancy. *Clin Sci (Colch)* 1994 Mar;86(3):251-5. PMID: 8156734. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
45. Brown MA, Buddle ML. Inadequacy of dipstick proteinuria in hypertensive pregnancy. *Aust N Z J Obstet Gynaecol* 1995 Nov;35(4):366-9. PMID: 8717555. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**

Appendix D. Excluded Studies

46. Brown MA, Buddle ML. Hypertension in pregnancy: maternal and fetal outcomes according to laboratory and clinical features. *Med J Aust* 1996 Oct 7;165(7):360-5. PMID: 8890841. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
47. Brown MA, Buddle ML, Farrell T, et al. Randomised trial of management of hypertensive pregnancies by Korotkoff phase IV or phase V. *Lancet* 1998 Sep 5;352(9130):777-81. PMID: 9737283. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
48. Brown MA, Robinson A, Bowyer L, et al. Ambulatory blood pressure monitoring in pregnancy: what is normal? *Am J Obstet Gynecol* 1998 Apr;178(4):836-42. PMID: 9579453. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
49. Brown MA, Robinson A, Buddle ML. Accuracy of automated blood pressure recorders in pregnancy. *Aust N Z J Obstet Gynaecol* 1998 Aug;38(3):262-5. PMID: 9761149. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
50. Brown MA, Robinson A, Jones M. The white coat effect in hypertensive pregnancy: much ado about nothing? *Br J Obstet Gynaecol* 1999 May;106(5):474-80. PMID: 10430198. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
51. Brown MA, Bowyer L, McHugh L, et al. Twenty-four-hour automated blood pressure monitoring as a predictor of preeclampsia. *Am J Obstet Gynecol* 2001 Sep;185(3):618-22. PMID: 11568788. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
52. Brown MA, Davis GK, McHugh L. The prevalence and clinical significance of nocturnal hypertension in pregnancy. *J Hypertens* 2001 Aug;19(8):1437-44. PMID: 11518852. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
53. Brown MA, McHugh L, Mangos G, et al. Automated self-initiated blood pressure or 24-hour ambulatory blood pressure monitoring in pregnancy? *BJOG* 2004 Jan;111(1):38-41. PMID: 14687050. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
54. Brown MA, Mangos G, Davis G, et al. The natural history of white coat hypertension during pregnancy. *BJOG* 2005 May;112(5):601-6. PMID: 15842284. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
55. Brown MA, Roberts L, Davis G, et al. Can we use the Omron T9P automated blood pressure monitor in pregnancy? *Hypertens Pregnancy* 2011;30(2):188-93. PMID: 20846049. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
56. Brown MA, Roberts LM, Mackenzie C, et al. A prospective randomized study of automated versus mercury blood pressure recordings in hypertensive pregnancy (PRAM Study). *Hypertens Pregnancy* 2012;31(1):107-19. PMID: 21219121. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
57. Brown MA. Is there a role for ambulatory blood pressure monitoring in pregnancy? *Clin Exp Pharmacol Physiol* 2014 Jan;41(1):16-21. PMID: 23651133. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
58. Bryant M, Santorelli G, Lawlor DA, et al. A comparison of South Asian specific and established BMI thresholds for determining obesity prevalence in pregnancy and predicting pregnancy complications: findings from the Born in Bradford cohort. *Int J Obes (Lond)* 2014 Mar;38(3):444-50. PMID: 23797188. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
59. Bullarbo M, Rylander R. Diastolic blood pressure increase is a risk indicator for pre-eclampsia. *Arch Gynecol Obstet* 2015 Apr;291(4):819-23. PMID: 25241271. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**

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60. Cade TJ, Gilbert SA, Polyakov A, et al. The accuracy of spot urinary protein-to-creatinine ratio in confirming proteinuria in pre-eclampsia. *Aust N Z J Obstet Gynaecol* 2012 Apr;52(2):179-82. PMID: 22335428. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
61. Campbell N, Ogle R, Thornton C, et al. Urinary placental growth factor differentiates the hypertensive disorders of pregnancy. *Aust N Z J Obstet Gynaecol* 2011 Dec;51(6):523-6. PMID: 21883135. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
62. Caradeux J, Serra R, Nien JK, et al. First trimester prediction of early onset preeclampsia using demographic, clinical, and sonographic data: a cohort study. *Prenat Diagn* 2013 Aug;33(8):732-6. PMID: 23584890. **KQ1E12, KQ1aE12, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
63. Caritis S, Sibai B, Hauth J, et al. Predictors of pre-eclampsia in women at high risk. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *Am J Obstet Gynecol* 1998 Oct;179(4):946-51. PMID: 9790376. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
64. Catov JM, Ness RB, Kip KE, et al. Risk of early or severe pre-eclampsia related to pre-existing conditions. *Int J Epidemiol* 2007 Apr;36(2):412-9. PMID: 17255351. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
65. Chan P, Brown M, Simpson JM, et al. Proteinuria in pre-eclampsia: how much matters? *BJOG* 2005 Mar;112(3):280-5. PMID: 15713140. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
66. Chappell LC, Seed PT, Myers J, et al. Exploration and confirmation of factors associated with uncomplicated pregnancy in nulliparous women: prospective cohort study. *BMJ* 2013;347:f6398. PMID: 24270055. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
67. Chappell LC, Bramham K, Shennan AH. Short-term prediction of preeclampsia: how close are we? *Biomark Med* 2014;8(4):455-8. PMID: 24796609. **KQ1E3, KQ1aE3, KQ2E3, KQ3E3, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
68. Chen BA, Parviainen K, Jeyabalan A. Correlation of catheterized and clean catch urine protein/creatinine ratios in preeclampsia evaluation. *Obstet Gynecol* 2008 Sep;112(3):606-10. PMID: 18757659. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4aE7, KQ4bE4, KQ4cE4, KQ5E4.**
69. Chen CL, Cheng Y, Wang PH, et al. Review of pre-eclampsia in Taiwan: a multi-institutional study. *Zhonghua Yi Xue Za Zhi (Taipei)* 2000 Dec;63(12):869-75. PMID: 11195137. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
70. Chen CY, Kwek K, Tan KH, et al. Our experience with eclampsia in Singapore. *Singapore Med J* 2003 Feb;44(2):88-93. PMID: 14503783. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
71. Chung Y, Brochut MC, Greeff A, et al. Clinical accuracy of inflationary oscillometry in pregnancy and pre-eclampsia: Omron-MIT Elite. *Pregnancy Hypertens* 2012;2(4):411-5. PMID: 26105612. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
72. Churchill D, Beevers DG. Differences between office and 24-hour ambulatory blood pressure measurement during pregnancy. *Obstet Gynecol* 1996 Sep;88(3):455-61. PMID: 8752258. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
73. Clark S, Hofmeyr GJ, Coats AJ, et al. Ambulatory blood pressure monitoring during pregnancy: validation of the TM-2420 monitor. *Obstet Gynecol* 1991 Jan;77(1):152-5. PMID: 1984216. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**

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74. Coghill AE, Hansen S, Littman AJ. Risk factors for eclampsia: a population-based study in Washington State, 1987-2007. *Am J Obstet Gynecol* 2011 Dec;205(6):553-7. PMID: 21855842. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
75. Cohen JL, Smilen KE, Bianco AT, et al. Predictive value of combined serum biomarkers for adverse pregnancy outcomes. *Eur J Obstet Gynecol Reprod Biol* 2014 Oct;181:89-94. PMID: 25129153. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
76. Combs CA, Wheeler BC, Kitzmiller JL. Urinary protein/creatinine ratio before and during pregnancy in women with diabetes mellitus. *Am J Obstet Gynecol* 1991 Oct;165(4:Pt 1):t-3. PMID: 1951554. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
77. Combs CA, Rosenn B, Kitzmiller JL, et al. Early-pregnancy proteinuria in diabetes related to preeclampsia. *Obstet Gynecol* 1993 Nov;82(5):802-7. PMID: 8414328. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E6, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
78. Cote AM, Firoz T, Mattman A, et al. The 24-hour urine collection: gold standard or historical practice? *Am J Obstet Gynecol* 2008 Dec;199(6):625-6. PMID: 18718568. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
79. Crovetto F, Figueras F, Triunfo S, et al. Added value of angiogenic factors for the prediction of early and late preeclampsia in the first trimester of pregnancy. *Fetal Diagn Ther* 2014;35(4):258-66. PMID: 24714555. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
80. Crovetto F, Figueras F, Crispi F, et al. Forms of Circulating Luteinizing Hormone Human Chorionic Gonadotropin Receptor for the Prediction of Early and Late Preeclampsia in the First Trimester of Pregnancy. *Fetal Diagn Ther* 2015 Feb 11 PMID: 25676660. **KQ1E12, KQ1aE12, KQ2E3, KQ3E3, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
81. Crovetto F, Figueras F, Triunfo S, et al. First trimester screening for early and late preeclampsia based on maternal characteristics, biophysical parameters, and angiogenic factors. *Prenat Diagn* 2015 Feb;35(2):183-91. PMID: 25346181. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
82. Cruz MO, Gao W, Hibbard JU. Obstetrical and perinatal outcomes among women with gestational hypertension, mild preeclampsia, and mild chronic hypertension. *Am J Obstet Gynecol* 2011 Sep;205(3):260-9. PMID: 22071056. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
83. Das V, Bhargava T, Das SK, et al. Microalbuminuria: a predictor of pregnancy-induced hypertension. *Br J Obstet Gynaecol* 1996 Sep;103(9):928-30. PMID: 8813317. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
84. Davis GK, Roberts LM, Mangos GJ, et al. Comparisons of auscultatory hybrid and automated sphygmomanometers with mercury sphygmomanometry in hypertensive and normotensive pregnant women: Parallel validation studies. *J Hypertens* 2015;33:499-506. PMID: 25380148. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
85. De Silva DA, Halstead AC, Cote AM, et al. Unexpected random urinary protein:creatinine ratio results-limitations of the pyrocatechol violet-dye method. *BMC Pregnancy Childbirth* 2013;13:152. PMID: 23865673. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE7, KQ4bE7, KQ4cE12, KQ5E12.**
86. De GA, Ghosh D, Anthony J, et al. Accuracy assessment of the Dinamap ProCare 400 in pregnancy and preeclampsia. *Hypertens Pregnancy* 2010 Jan;29(2):198-205. PMID: 20367507. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
87. Deis S, Rouzier R, Kayem G, et al. Development of a nomogram to predict occurrence of preeclampsia. *Eur J Obstet Gynecol Reprod Biol* 2008 Apr;137(2):146-51. PMID: 17669579. **KQ1E12, KQ1aE12, KQ2E3, KQ3E3, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**

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88. Delic R, Stefanovic M. Optimal laboratory panel for predicting preeclampsia. *J Matern Fetal Neonatal Med* 2010 Jan;23(1):96-102. PMID: 19658035. **KQ1E2, KQ1aE2, KQ2E3, KQ3E3, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
89. Demirci O, Kumru P, Arinkan A, et al. Spot protein/creatinine ratio in preeclampsia as an alternative for 24-hour urine protein. *Balkan Med J* 2015 Jan;32(1):51-5. PMID: 25759772. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
90. Di Lorenzo G, Ceccarello M, Cecotti V, et al. First trimester maternal serum PIGF, free beta-hCG, PAPP-A, PP-13, uterine artery Doppler and maternal history for the prediction of preeclampsia. *Placenta* 2012 Jun;33(6):495-501. PMID: 22459245. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
91. Duggan PM. Which Korotkoff sound should be used for the diastolic blood pressure in pregnancy? *Aust N Z J Obstet Gynaecol* 1998 May;38(2):194-7. PMID: 9653859. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
92. Duggan PM. Quiet resting is not necessary prior to routine antenatal blood pressure measurement. *Aust N Z J Obstet Gynaecol* 1999 Feb;39(1):19-20. PMID: 10099741. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
93. Dunsmuir DT, Payne BA, Cloete G, et al. Development of mHealth applications for pre-eclampsia triage. *IEEE J Biomed Health Inform* 2014 Nov;18(6):1857-64. PMID: 25375683. **KQ1E1, KQ1aE1, KQ2E1, KQ3E1, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
94. Durnwald C, Mercer B. A prospective comparison of total protein/creatinine ratio versus 24-hour urine protein in women with suspected preeclampsia. *Am J Obstet Gynecol* 2003 Sep;189(3):848-52. PMID: 14526328. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4bE4, KQ4cE4, KQ5E4.**
95. Dwyer BK, Gorman M, Carroll IR, et al. Urinalysis vs urine protein-creatinine ratio to predict significant proteinuria in pregnancy. *J Perinatol* 2008 Jul;28(7):461-7. PMID: 18288120. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4bE4, KQ4cE4, KQ5E4.**
96. Ekholm E, Erkkola R, Hartiala J. Comparison of cardiovascular reflex tests and blood pressure measurement in prediction of pregnancy-induced hypertension. *Eur J Obstet Gynecol Reprod Biol* 1994 Mar 31;54(1):37-41. PMID: 8045331. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
97. Elvan-Taspinar A, Uiterkamp LA, Sikkema JM, et al. Validation and use of the Finometer for blood pressure measurement in normal, hypertensive and pre-eclamptic pregnancy. *J Hypertens* 2003 Nov;21(11):2053-60. PMID: 14597848. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
98. Emonts P, Seaksan S, Seidel L, et al. Prediction of maternal predisposition to preeclampsia. *Hypertens Pregnancy* 2008;27(3):237-45. PMID: 18696352. **KQ1E2, KQ1aE2, KQ2E2, KQ3E2, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
99. Eskenazi B, Fenster L, Sidney S. A multivariate analysis of risk factors for preeclampsia. *JAMA* 1991 Jul 10;266(2):237-41. PMID: 2056625. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
100. Eslamian L, Behnam F, Tehrani ZF, et al. Random urine protein creatinine ratio as a preadmission test in hypertensive pregnancies with urinary protein creatinine ratio. *Acta Med Iran* 2011;49(2):81-4. PMID: 21598214. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
101. Farina A, Rapacchia G, Freni SA, et al. Prospective evaluation of ultrasound and biochemical-based multivariable models for the prediction of late pre-eclampsia. *Prenat Diagn* 2011 Dec;31(12):1147-52. PMID: 22009522. **KQ1E12, KQ1aE12, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**

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102. Ferrazzani S, Caruso A, De CS, et al. Proteinuria and outcome of 444 pregnancies complicated by hypertension. *Am J Obstet Gynecol* 1990 Feb;162(2):366-71. PMID: 2309816. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
103. Flores L, Levy I, Aguilera E, et al. Usefulness of ambulatory blood pressure monitoring in pregnant women with type 1 diabetes. *Diabetes Care* 1999 Sep;22(9):1507-11. PMID: 10480517. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
104. Fong A, Chau CT, Pan D, et al. Clinical morbidities, trends, and demographics of eclampsia: a population-based study. *Am J Obstet Gynecol* 2013 Sep;209(3):229-7. PMID: 23727516. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
105. Forest JC, Masse J, Bujold E, et al. PP054. Predicting preeclampsia at late mid-term pregnancy before occurrence of clinical symptoms: Clinical utility of biomarkers and clinical parameters in a low-risk population. *Pregnancy Hypertens* 2012 Jul;2(3):271. PMID: 26105377. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
106. Forest JC, Masse J, Bujold E, et al. OS090. Performance of candidate clinical and biochemical markers in screening early in pregnancy to detect women at high risk to develop preeclampsia. *Pregnancy Hypertens* 2012 Jul;2(3):227. PMID: 26105305. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
107. Franceschini N, Savitz DA, Kaufman JS, et al. Maternal urine albumin excretion and pregnancy outcome. *Am J Kidney Dis* 2005 Jun;45(6):1010-8. PMID: 15957129. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E4.**
108. Franx A, van der Post JA, Elfering IM, et al. Validation of automated blood pressure recording in pregnancy. *Br J Obstet Gynaecol* 1994 Jan;101(1):66-9. PMID: 8297873. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
109. Gaillard R, Bakker R, Willemsen SP, et al. Blood pressure tracking during pregnancy and the risk of gestational hypertensive disorders: the Generation R Study. *Eur Heart J* 2011 Dec;32(24):3088-97. PMID: 21821845. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
110. Gallo DM, Poon LC, Akolekar R, et al. Prediction of preeclampsia by uterine artery Doppler at 20-24 weeks' gestation. *Fetal Diagn Ther* 2013;34(4):241-7. PMID: 24192614. **KQ1E12, KQ1aE12, KQ2E3, KQ3E3, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
111. Gangaram R, Naicker M, Moodley J. Comparison of pregnancy outcomes in women with hypertensive disorders of pregnancy using 24-hour urinary protein and urinary microalbumin to creatinine ratio. *Int J Gynaecol Obstet* 2009 Oct;107(1):19-22. PMID: 19666171. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
112. Gangaram R, Naicker M, Moodley J. Accuracy of the spot urinary microalbumin:creatinine ratio and visual dipsticks in hypertensive pregnant women. *Eur J Obstet Gynecol Reprod Biol* 2009 Jun;144(2):146-8. PMID: 19371998. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
113. Garcia-Tizon LS, Tayyar A, Poon LC, et al. Competing risks model in screening for preeclampsia by biophysical and biochemical markers at 30-33 weeks' gestation. *Fetal Diagn Ther* 2014;36(1):9-17. PMID: 24902880. **KQ1E3, KQ1aE3, KQ2E3, KQ3E3, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
114. Giguere Y, Masse J, Theriault S, et al. Screening for pre-eclampsia early in pregnancy: performance of a multivariable model combining clinical characteristics and biochemical markers. *BJOG* 2015 Feb;122(3):402-10. PMID: 25175335. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**

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115. Ginsberg JM, Chang BS, Matarese RA, et al. Use of single voided urine samples to estimate quantitative proteinuria. *N Engl J Med* 1983 Dec 22;309(25):1543-6. PMID: 6656849. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
116. Giurgescu C, Sanguanklin N, England CG, et al. Relationships among psychosocial factors, biomarkers, preeclampsia, and preterm birth in African American women: a pilot. *Appl Nurs Res* 2015 Feb;28(1):e1-e6. PMID: 25282477. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
117. Goetzinger KR, Singla A, Gerkowicz S, et al. Predicting the risk of pre-eclampsia between 11 and 13 weeks' gestation by combining maternal characteristics and serum analytes, PAPP-A and free beta-hCG. *Prenat Diagn* 2010 Dec;30(12-13):1138-42. PMID: 20936638. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
118. Goetzinger KR, Tuuli MG, Cahill AG, et al. Development and Validation of a Risk Factor Scoring System for First-Trimester Prediction of Preeclampsia. *Am J Perinatol* 2014 Apr 4;31(12):1049-56. PMID: 24705967. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
119. Golar M, Benedict A, Jones C, et al. Inflationary oscillometry provides accurate measurement of blood pressure in pre-eclampsia. *BJOG* 2002 Oct;109(10):1143-7. PMID: 12387468. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
120. Greeley ET, Terry KL, Spencer JV. [257-POS]: Risk of gestational hypertension in relation to number of prenatal visits. *Pregnancy Hypertens* 2015 Jan;5(1):129. PMID: 25787606. **KQ1E11, KQ1aE11, KQ2E11, KQ3E11, KQ4E11, KQ4aE11, KQ4bE11, KQ4cE11, KQ5E11.**
121. Greeley ET, Terry KL, Spencer JV. [251-POS]: Risk of eclampsia compared to number of prenatal visits. *Pregnancy Hypertens* 2015 Jan;5(1):126-7. PMID: 25787601. **KQ1E11, KQ1aE11, KQ2E11, KQ3E11, KQ4E11, KQ4aE11, KQ4bE11, KQ4cE11, KQ5E11.**
122. Green LA, Froman RD. Blood pressure measurement during pregnancy: auscultatory versus oscillatory methods. *J Obstet Gynecol Neonatal Nurs* 1996 Feb;25(2):155-9. PMID: 8656306. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
123. Gribble RK, Fee SC, Berg RL. The value of routine urine dipstick screening for protein at each prenatal visit. *Am J Obstet Gynecol* 1995 Jul;173(1):214-7. PMID: 7631685. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E3, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
124. Grobman WA, Bailit J.L., Rice M.M, et al. Frequency of and factors associated with severe maternal morbidity. *Obstet Gynecol* 2014;123(4):804-10. PMID: None. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
125. Gupta M, Shennan AH, Halligan A, et al. Accuracy of oscillometric blood pressure monitoring in pregnancy and pre-eclampsia. *Br J Obstet Gynaecol* 1997 Mar;104(3):350-5. PMID: 9091015. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
126. Gurgel Alves JA, Praciano de Sousa PC, Bezerra Maia E Holanda Moura, et al. First-trimester maternal ophthalmic artery Doppler analysis for prediction of pre-eclampsia. *Ultrasound Obstet Gynecol* 2014 Oct;44(4):411-8. PMID: 24585555. **KQ1E1, KQ1aE1, KQ2E1, KQ3E1, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
127. Haas DM, Sabi F, McNamara M, et al. Comparing ambulatory spot urine protein/creatinine ratios and 24-h urine protein measurements in normal pregnancies. *J Matern Fetal Neonatal Med* 2003 Oct;14(4):233-6. PMID: 14738168. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE3, KQ4cE4, KQ5E4.**
128. Haas DM, Parker CB, Wing DA, et al. A description of the methods of the Nulliparous Pregnancy Outcomes Study: monitoring mothers-to-be (nuMoM2b). *Am J Obstet Gynecol* 2015 Apr;212(4):539. PMID: 25648779. **KQ1E12, KQ1aE12, KQ2E3, KQ3E3, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**

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129. Hallak M, Bottoms SF, Knudson K, et al. Determining blood pressure in pregnancy. Positional hydrostatic effects. *J Reprod Med* 1997 Jun;42(6):333-6. PMID: 9219119. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
130. Harris JM, Franck L, Green B, et al. The psychological impact of providing women with risk information for pre-eclampsia: A qualitative study. *Midwifery* 2014 Apr 30;30(12):1187-95. PMID: 24917032. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
131. Hasslacher C. Clinical significance of microalbuminuria and evaluation of the Micral-Test. *Clin Biochem* 1993 Aug;26(4):283-7. PMID: 8242889. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
132. Hedderson MM, Darbinian JA, Sridhar SB, et al. Prepregnancy cardiometabolic and inflammatory risk factors and subsequent risk of hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 2012 Jul;207(1):68-9. PMID: 22727352. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
133. Hermida RC, Ayala DE, Mojon A, et al. High sensitivity test for the early diagnosis of gestational hypertension and preeclampsia. II. Circadian blood pressure variability in health and hypertensive pregnant women. *J Perinat Med* 1997;25(2):153-67. PMID: 9189835. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
134. Hermida RC, Ayala DE, Mojon A, et al. High sensitivity test for the early diagnosis of gestational hypertension and preeclampsia. I. Predictable variability of cardiovascular characteristics during gestation in healthy and hypertensive pregnant women. *J Perinat Med* 1997;25(1):101-9. PMID: 9085211. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
135. Hermida RC, Ayala DE. Diagnosing gestational hypertension and preeclampsia with the 24-hour mean of blood pressure. *Hypertension* 1997 Dec;30(6):1531-7. PMID: 9403578. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
136. Hermida RC, Ayala DE, Mojon A, et al. Blood pressure excess for the early identification of gestational hypertension and preeclampsia. *Hypertension* 1998 Jan;31(1):83-9. PMID: 9449396. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
137. Hermida RC, Ayala DE, Mojon A, et al. Blood pressure patterns in normal pregnancy, gestational hypertension, and preeclampsia. *Hypertension* 2000 Aug;36(2):149-58. PMID: 10948070. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
138. Hermida RC, Ayala DE, Iglesias M. Predictable blood pressure variability in healthy and complicated pregnancies. *Hypertension* 2001 Sep;38(3:Pt 2):t-41. PMID: 11566967. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
139. Hermida RC, Ayala DE. Evaluation of the blood pressure load in the diagnosis of hypertension in pregnancy. *Hypertension* 2001 Sep;38(3:Pt 2):t-9. PMID: 11566965. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
140. Hermida RC, Ayala DE. Prognostic value of office and ambulatory blood pressure measurements in pregnancy. *Hypertension* 2002 Sep;40(3):298-303. PMID: 12215470. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
141. Hermida RC, Ayala DE. Sampling requirements for ambulatory blood pressure monitoring in the diagnosis of hypertension in pregnancy. *Hypertension* 2003 Oct;42(4):619-24. PMID: 12939237. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**

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142. Hermida RC, Ayala DE, Mojon A, et al. Differences in circadian blood pressure variability during gestation between healthy and complicated pregnancies. *Am J Hypertens* 2003 Mar;16(3):200-8. PMID: 12620698. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
143. Hermida RC, Ayala DE, Iglesias M. Circadian rhythm of blood pressure challenges office values as the "gold standard" in the diagnosis of gestational hypertension. *Chronobiol Int* 2003 Jan;20(1):135-56. PMID: 12638696. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
144. Hermida RC, Ayala DE, Iglesias M. Differences in circadian pattern of ambulatory pulse pressure between healthy and complicated pregnancies. *Hypertension* 2004 Sep;44(3):316-21. PMID: 15289468. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
145. Hermida RC, Ayala DE. Reference thresholds for 24-h, diurnal, and nocturnal ambulatory blood pressure mean values in pregnancy. *Blood Press Monit* 2005 Feb;10(1):33-41. PMID: 15687872. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
146. Herraiz I, Arbues J, Camano I, et al. Application of a first-trimester prediction model for pre-eclampsia based on uterine arteries and maternal history in high-risk pregnancies. *Prenat Diagn* 2009 Dec;29(12):1123-9. PMID: 19813221. **KQ1E12, KQ1aE12, KQ2E2, KQ3E2, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
147. Higgins JR, Walshe JJ, Halligan A, et al. Can 24-hour ambulatory blood pressure measurement predict the development of hypertension in primigravidae? *Br J Obstet Gynaecol* 1997 Mar;104(3):356-62. PMID: 9091016. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E3, KQ4aE4, KQ4bE3, KQ4cE4, KQ5E4.**
148. Hirashima C, Ohkuchi A, Takahashi K, et al. A novel three-step approach for predicting the imminent onset of preeclampsia within 4 weeks after blood sampling at 19-31 weeks of gestation. *Hypertens Res* 2014 Jun;37(6):519-25. PMID: 24599015. **KQ1E3, KQ1aE3, KQ2E3, KQ3E3, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
149. Hirshberg A, Draper J, Curley C, et al. A random protein-creatinine ratio accurately predicts baseline proteinuria in early pregnancy. *J Matern Fetal Investig* 2014 Dec;27(18):1834-8. PMID: 24660896. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE10, KQ4bE4, KQ4cE4, KQ5E12.**
150. Homer CS, Brown MA, Mangos G, et al. Non-proteinuric pre-eclampsia: a novel risk indicator in women with gestational hypertension. *J Hypertens* 2008 Feb;26(2):295-302. PMID: 18192844. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
151. Hooper DE. Detecting GD and preeclampsia. Effectiveness of routine urine screening for glucose and protein. *J Reprod Med* 1996 Dec;41(12):885-8. PMID: 8979200. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE7, KQ4bE4, KQ4cE4, KQ5E4.**
152. Hossain N, Khan N, Shah N, et al. Spot urine protein-creatinine ratio and 24-h urine protein excretion: Diagnostic accuracy in women with pre-eclampsia. *Pregnancy Hypertens* 2014 Jan;4(1):87-90. PMID: 26104260. **KQ1E1, KQ1aE1, KQ2E1, KQ3E1, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
153. Huang Q, Gao Y, Yu Y, et al. Urinary spot albumin:creatinine ratio for documenting proteinuria in women with preeclampsia. *Rev Obstet Gynecol* 2012;5(1):9-15. PMID: 22582122. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
154. Irgens-Moller L, Hemmingsen L, Holm J. Diagnostic value of microalbuminuria in pre-eclampsia. *Clin Chim Acta* 1986 Jun 30;157(3):295-8. PMID: 3731490. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**

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155. Ishikuro M, Obara T, Metoki H, et al. Blood pressure measured in the clinic and at home during pregnancy among nulliparous and multiparous women: the BOSHI study. *Am J Hypertens* 2013 Jan;26(1):141-8. PMID: 23382338. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
156. Izumi A, Minakami H, Kuwata T, et al. Calcium-to-creatinine ratio in spot urine samples in early pregnancy and its relation to the development of preeclampsia. *Metabolism* 1997 Oct;46(10):1107-8. PMID: 9322789. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE4, KQ4cE4, KQ5E4.**
157. Jacobs DJ, Vreeburg SA, Dekker GA, et al. Risk factors for hypertension during pregnancy in South Australia. *Aust N Z J Obstet Gynaecol* 2003 Dec;43(6):421-8. PMID: 14712944. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
158. Jain L. Effect of pregnancy-induced and chronic hypertension on pregnancy outcome. *J Perinatol* 1997 Nov;17(6):425-7. PMID: 9447526. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
159. Jaschevatzky OE, Rosenberg RP, Shalit A, et al. Protein/creatinine ratio in random urine specimens for quantitation of proteinuria in preeclampsia. *Obstet Gynecol* 1990 Apr;75(4):604-6. PMID: 2314778. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
160. Juarez SP, Wagner P, Merlo J. Applying measures of discriminatory accuracy to revisit traditional risk factors for being small for gestational age in Sweden: a national cross-sectional study. *BMJ Open* 2014;4(7):e005388. PMID: 25079936. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
161. Jwa SC, Arata N, Sakamoto N, et al. Prediction of pregnancy-induced hypertension by a shift of blood pressure class according to the JSH 2009 guidelines. *Hypertens Res* 2011 Nov;34(11):1203-8. PMID: 21796130. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
162. Kayatas S, Erdogdu E, Cakar E, et al. Comparison of 24-hour urinary protein and protein-to-creatinine ratio in women with preeclampsia. *Eur J Obstet Gynecol Reprod Biol* 2013 Oct;170(2):368-71. PMID: 23928475. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
163. Kenny LC, Black MA, Poston L, et al. Early pregnancy prediction of preeclampsia in nulliparous women, combining clinical risk and biomarkers: The Screening for Pregnancy Endpoints (SCOPE) international cohort study. *Hypertension* 2014;64:644-52. PMID: 25122928. **KQ1E12, KQ1aE12, KQ2E3, KQ3E3, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
164. Kieler H, Zettergren T, Svensson H, et al. Assessing urinary albumin excretion in pre-eclamptic women: which sample to use? *BJOG* 2003 Jan;110(1):12-7. PMID: 12504929. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
165. Kitzman H, Olds DL, Henderson CR, Jr., et al. Effect of prenatal and infancy home visitation by nurses on pregnancy outcomes, childhood injuries, and repeated childbearing. A randomized controlled trial. *JAMA* 1997 Aug 27;278(8):644-52. PMID: 9272896. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
166. Kleinrouweler CE, Mol BW. Clinical prediction models for pre-eclampsia: time to take the next step. *Ultrasound Obstet Gynecol* 2014 Sep;44(3):249-51. PMID: 25154485. **KQ1E3, KQ1aE3, KQ2E3, KQ3E3, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
167. Klungsoyr K, Morken NH, Irgens L, et al. Secular trends in the epidemiology of pre-eclampsia throughout 40 years in Norway: prevalence, risk factors and perinatal survival. *Paediatr Perinat Epidemiol* 2012 May;26(3):190-8. PMID: 22471678. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**

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168. Knuist M, Bonsel GJ, Zondervan HA, et al. Intensification of fetal and maternal surveillance in pregnant women with hypertensive disorders. *Int J Gynaecol Obstet* 1998 May;61(2):127-33. PMID: 9639216. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
169. Koenen SV, Franx A, Oosting H, et al. Within-subject variability of differences between conventional and automated blood pressure measurements in pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1998 Sep;80(1):79-84. PMID: 9758265. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
170. Kolialexi A, Gourgiotis D, Daskalakis G, et al. Validation of serum biomarkers derived from proteomic analysis for the early screening of preeclampsia. *Dis Markers* 2015;2015:121848. PMID: 25628472. **KQ1E12, KQ1aE12, KQ2E3, KQ3E3, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
171. Konstantin-Hansen KF, Hesseldahl H, Pedersen SM. Microalbuminuria as a predictor of preeclampsia. *Acta Obstet Gynecol Scand* 1992 Jul;71(5):343-6. PMID: 1326208. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
172. Kraus M, Nicolaides K. Identifying risks for early onset pre-eclampsia. *Women's health* 2015 Jan;11(1):15-7. PMID: 25581051. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
173. Kuc S, Koster MP, Franx A, et al. Maternal characteristics, mean arterial pressure and serum markers in early prediction of preeclampsia. *PLoS One* 2013;8(5):e63546. PMID: 23717445. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
174. Kuo VS, Koumantakis G, Gallery ED. Proteinuria and its assessment in normal and hypertensive pregnancy. *Am J Obstet Gynecol* 1992 Sep;167(3):723-8. PMID: 1530030. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
175. Kuromoto K, Watanabe M, Adachi K, et al. Increases in urinary creatinine and blood pressure during early pregnancy in pre-eclampsia. *Ann Clin Biochem* 2010 Jul;47(Pt:4):4-42. PMID: 20511374. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
176. Kwek K, Chan YG, Tan KH, et al. Validation of an oscillometric electronic sphygmomanometer in an obstetric population. *Am J Hypertens* 1998 Aug;11(8Pt 1):t-82. PMID: 9715791. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
177. Kyle PM, Clark SJ, Buckley D, et al. Second trimester ambulatory blood pressure in nulliparous pregnancy: a useful screening test for pre-eclampsia? *Br J Obstet Gynaecol* 1993 Oct;100(10):914-9. PMID: 8217973. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
178. Kyle PM, Fielder JN, Pullar B, et al. Comparison of methods to identify significant proteinuria in pregnancy in the outpatient setting. *BJOG* 2008 Mar;115(4):523-7. PMID: 18201282. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4bE4, KQ4cE3, KQ5E4.**
179. LA BM, Okido MM, Barbieri MA, et al. [240-POS]: Risk factors influencing the development of hypertension in pregnancy in a convenience cohort. *Pregnancy Hypertens* 2015 Jan;5(1):121. PMID: 25787590. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
180. Lai J, Poon LC, Bakalis S, et al. Systolic, diastolic and mean arterial pressure at 30-33 weeks in the prediction of preeclampsia. *Fetal Diagn Ther* 2013;33(3):173-81. PMID: 23328077. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E3, KQ4aE4, KQ4bE3, KQ4cE4, KQ5E4.**
181. Lamontagne A, Cote AM, Rey E. The urinary protein-to-creatinine ratio in Canadian women at risk of preeclampsia: does the time of day of testing matter? *J Obstet Gynaecol Can* 2014 Apr;36(4):303-8. PMID: 24798667. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4bE2, KQ4cE2, KQ5E2.**

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182. Lan PG, Clayton PA, Hyett J, et al. Measuring blood pressure in pregnancy and postpartum: assessing the reliability of automated measuring devices. *Hypertens Pregnancy* 2013 Dec 4;33(2):168-76. PMID: 24304096. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
183. Lauszus FF, Rasmussen OW, Lousen T, et al. Ambulatory blood pressure as predictor of preeclampsia in diabetic pregnancies with respect to urinary albumin excretion rate and glycemic regulation. *Acta Obstet Gynecol Scand* 2001 Dec;80(12):1096-103. PMID: 11846705. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
184. Lauszus FF, Rosgaard A, Lousen T, et al. Precision, consistency, and reproducibility of blood pressure in diabetic and non-diabetic pregnancy: the appraisal of repeated measurements. *Acta Obstet Gynecol Scand* 2007;86(9):1063-70. PMID: 17712646. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
185. Lauszus FF, Rosgaard A, Lousen T, et al. Night/day ratio as predictor of preeclampsia in normoalbuminuric, diabetic women: early signs of blood pressure disorders. *Arch Gynecol Obstet* 2009 Jun;279(6):829-34. PMID: 19018544. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E12, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E4.**
186. Leanos-Miranda A, Marquez-Acosta J, Romero-Arauz F, et al. Protein:creatinine ratio in random urine samples is a reliable marker of increased 24-hour protein excretion in hospitalized women with hypertensive disorders of pregnancy. *Clin Chem* 2007 Sep;53(9):1623-8. PMID: 17660273. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
187. Lee AM, Briandet BM, Zelig CM. Adverse pregnancy outcomes in hypertensive patients: predictive value of protein concentration versus total protein. *J Matern Fetal Neonatal Med* 2014 Feb 3;27(16):1643-5. PMID: 24484078. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E4.**
188. Lee LC, Sheu BC, Shau WY, et al. Mid-trimester beta-hCG levels incorporated in a multifactorial model for the prediction of severe pre-eclampsia. *Prenat Diagn* 2000 Sep;20(9):738-43. PMID: 11015703. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
189. Leeners B, Stiller R, Neumaier-Wagner P, et al. Psychosocial distress associated with treatment of hypertensive diseases in pregnancy. *Psychosomatics* 2008 Sep;49(5):413-9. PMID: 18794510. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
190. Leung C, Saaid R, Pedersen L, et al. Demographic factors that can be used to predict early-onset pre-eclampsia. *J Matern Fetal Neonatal Med* 2014 Jun 5;28(5):535-9. PMID: 24827601. **KQ1E4, KQ1aE4, KQ2E13, KQ3E4, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
191. Levine RJ, Ewell MG, Hauth JC, et al. Should the definition of preeclampsia include a rise in diastolic blood pressure of ≥ 15 mm Hg to a level < 90 mm Hg in association with proteinuria? *Am J Obstet Gynecol* 2000 Oct;183(4):787-92. PMID: 11035314. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
192. Li N, Ghosh G, Gudmundsson S. Uterine artery Doppler in high-risk pregnancies at 23-24 gestational weeks is of value in predicting adverse outcome of pregnancy and selecting cases for more intense surveillance. *Acta Obstet Gynecol Scand* 2014 Dec;93(12):1276-81. PMID: 25155650. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
193. Liro M, Gasowski J, Wydra D, et al. Twenty-four-hour and conventional blood pressure components and risk of preterm delivery or neonatal complications in gestational hypertension. *Blood Press* 2009;18(1-2):36-43. PMID: 19353410. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**

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194. Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. *Am J Obstet Gynecol* 2013 Dec;209(6):544. PMID: 23973398. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
195. Liu CM, Cheng PJ, Chang SD. Maternal complications and perinatal outcomes associated with gestational hypertension and severe preeclampsia in Taiwanese women. *J Formos Med Assoc* 2008 Feb;107(2):129-38. PMID: 18285245. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
196. Liu S, Joseph KS, Liston RM, et al. Incidence, risk factors, and associated complications of eclampsia. *Obstet Gynecol* 2011 Nov;118(5):987-94. PMID: 22015865. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
197. Llorba E, Carreras E, Gratacos E, et al. Maternal history and uterine artery Doppler in the assessment of risk for development of early- and late-onset preeclampsia and intrauterine growth restriction. *Obstet Gynecol Int* 2009;2009:275613. PMID: 19936122. **KQ1E3, KQ1aE3, KQ2E3, KQ3E3, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
198. Lo C, Taylor RS, Gamble G, et al. Use of automated home blood pressure monitoring in pregnancy: is it safe? *Am J Obstet Gynecol* 2002 Nov;187(5):1321-8. PMID: 12439526. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
199. Loi K, Khoo CK, Tan KH, et al. A review of 93 cases of severe preeclampsia in Singapore: are there risk factors for complications? *Singapore Med J* 2007 Sep;48(9):808-12. PMID: 17728960. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
200. Lopez MC, Belizan JM, Villar J, et al. The measurement of diastolic blood pressure during pregnancy: which Korotkoff phase should be used? *Am J Obstet Gynecol* 1994 Feb;170(2):574-8. PMID: 8116715. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E3, KQ4aE4, KQ4bE3, KQ4cE4, KQ5E4.**
201. Magee LA, von DP, Bohun CM, et al. Serious perinatal complications of non-proteinuric hypertension: an international, multicentre, retrospective cohort study. *J Obstet Gynaecol Can* 2003 May;25(5):372-82. PMID: 12738978. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E4.**
202. Magnussen EB, Vatten LJ, Lund-Nilsen TI, et al. Prepregnancy cardiovascular risk factors as predictors of pre-eclampsia: population based cohort study. *BMJ* 2007 Nov 10;335(7627):978. PMID: 17975256. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
203. Mahmoudi N, Graves SW, Solomon CG, et al. Eclampsia: a 13-year experience at a United States tertiary care center. *J Womens Health Gend Based Med* 1999 May;8(4):495-500. PMID: 10839704. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
204. Makihara N, Yamasaki M, Morita H, et al. A dipstick test combined with urine specific gravity improved the accuracy of proteinuria determination in pregnancy screening. *Kobe J Med Sci* 2011;56(4):E165-E172. PMID: 21937864. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
205. Martins-Costa SH, Vettorazzi J, Valerio E, et al. Protein creatinine ratio in random urine sample of hypertensive pregnant women: maternal and perinatal outcomes. *Hypertens Pregnancy* 2011;30(3):331-7. PMID: 21174587. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
206. Mbah AK, Alio AP, Marty PJ, et al. Recurrent versus isolated pre-eclampsia and risk of fetoinfant morbidity outcomes: racial/ethnic disparity. *Eur J Obstet Gynecol Reprod Biol* 2011 May;156(1):23-8. PMID: 21316142. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**

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207. McCowan LM, Thompson JM, Taylor RS, et al. Clinical prediction in early pregnancy of infants small for gestational age by customised birthweight centiles: findings from a healthy nulliparous cohort. *PLoS One* 2013;8(8):e70917. PMID: 23940665. **KQ1E4, KQ1aE4, KQ2E4, KQ3E4, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
208. McDuffie RS, Jr., Beck A, Bischoff K, et al. Effect of frequency of prenatal care visits on perinatal outcome among low-risk women. A randomized controlled trial. *JAMA* 1996 Mar 20;275(11):847-51. PMID: 8596222. **KQ1E7, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4.**
209. Mello G, Parretti E, Cioni R, et al. Individual longitudinal patterns in biochemical and hematological markers for the early prediction of pre-eclampsia. *J Matern Fetal Neonatal Med* 2002 Feb;11(2):93-9. PMID: 12375550. **KQ1E2, KQ1aE2, KQ2E3, KQ3E3, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
210. Meyer NL, Mercer BM, Friedman SA, et al. Urinary dipstick protein: a poor predictor of absent or severe proteinuria. *Am J Obstet Gynecol* 1994 Jan;170(1:Pt 1):t-41. PMID: 8296815. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4aE2, KQ4bE4, KQ4cE4, KQ5E4.**
211. Millar JG, Campbell SK, Albano JD, et al. Early prediction of pre-eclampsia by measurement of kallikrein and creatinine on a random urine sample. *Br J Obstet Gynaecol* 1996 May;103(5):421-6. PMID: 8624314. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
212. Mittendorf R, Lain KY, Williams MA, et al. Preeclampsia. A nested, case-control study of risk factors and their interactions. *J Reprod Med* 1996 Jul;41(7):491-6. PMID: 8829061. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
213. Mohseni SM, Moez N, Naghizadeh MM, et al. Correlation of random urinary protein to creatinine ratio in 24-hour urine samples of pregnant women with preeclampsia. *J Family Reprod Health* 2013 Jun;7(2):95-101. PMID: 24971109. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
214. Moon M, Odibo A. First-trimester screening for preeclampsia: impact of maternal parity on modeling and screening effectiveness. *J Matern Fetal Neonatal Med* 2014 Nov 11:1-6. PMID: 25330843. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
215. Morikawa M, Cho K, Yamada T, et al. Risk factors for eclampsia in Japan between 2005 and 2009. *Int J Gynaecol Obstet* 2012 Apr;117(1):66-8. PMID: 22257769. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
216. Mostello D, Catlin TK, Roman L, et al. Preeclampsia in the parous woman: who is at risk? *Am J Obstet Gynecol* 2002 Aug;187(2):425-9. PMID: 12193937. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
217. Moura SB EH, Park F, Murthi P, et al. TNF-R1 as a first trimester marker for prediction of pre-eclampsia. *J Matern Fetal Neonatal Med* 2015 Mar 17:1-7. PMID: 25758630. **KQ1E12, KQ1aE12, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
218. Moutquin JM, Rainville C, Giroux L, et al. Is a threshold increase in blood pressure predictive of preeclampsia? A prospective cohort study. *Clin Exp Hypertens B* 1990;9(2):225-35. PMID: None. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E3, KQ4aE4, KQ4bE3, KQ4cE4, KQ5E4.**
219. Murray N, Homer CS, Davis GK, et al. The clinical utility of routine urinalysis in pregnancy: a prospective study. *Med J Aust* 2002 Nov 4;177(9):477-80. PMID: 12405888. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE7, KQ4bE3, KQ4cE3, KQ5E4.**
220. Myatt L, Clifton RG, Roberts JM, et al. First-trimester prediction of preeclampsia in nulliparous women at low risk. *Obstet Gynecol* 2012 Jun;119(6):1234-42. PMID: 22617589. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**

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221. Myers J, Tuytten R, Thomas G, et al. OS043. Identification and validation of novel markers for the prediction of pre-eclampsia. *Pregnancy Hypertens* 2012 Jul;2(3):200. PMID: 26105257. **KQ1E12, KQ1aE12, KQ2E3, KQ3E3, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
222. Myers JE, Kenny LC, McCowan LM, et al. P30. Angiogenic factors combined with clinical risk factors to predict preterm preeclampsia in nulliparous women. *Pregnancy Hypertens* 2011 Jul;1(3-4):286-7. PMID: 26009120. **KQ1E1, KQ1aE1, KQ2E1, KQ3E1, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
223. Myers JE, Kenny LC, McCowan LM, et al. Angiogenic factors combined with clinical risk factors to predict preterm pre-eclampsia in nulliparous women: a predictive test accuracy study. *BJOG* 2013 Sep;120(10):1215-23. PMID: 23906160. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
224. Nakamura T, Ito M, Yoshimura T, et al. Usefulness of the urinary microalbumin/creatinine ratio in predicting pregnancy-induced hypertension. *Int J Gynaecol Obstet* 1992 Feb;37(2):99-103. PMID: 1348709. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4aE6, KQ4bE4, KQ4cE4, KQ5E4.**
225. Natarajan P, Shennan AH, Penny J, et al. Comparison of auscultatory and oscillometric automated blood pressure monitors in the setting of preeclampsia. *Am J Obstet Gynecol* 1999 Nov;181(5:Pt 1):t-10. PMID: 10561646. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
226. Neithardt AB, Dooley SL, Borensztajn J. Prediction of 24-hour protein excretion in pregnancy with a single voided urine protein-to-creatinine ratio. *Am J Obstet Gynecol* 2002 May;186(5):883-6. PMID: 12015502. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E2.**
227. Nijdam ME, Janssen KJ, Moons KG, et al. Prediction model for hypertension in pregnancy in nulliparous women using information obtained at the first antenatal visit. *J Hypertens* 2010 Jan;28(1):119-26. PMID: 19907344. **KQ1E12, KQ1aE12, KQ2E4, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
228. Nisell H, Trygg M, Back R. Urine albumin/creatinine ratio for the assessment of albuminuria in pregnancy hypertension. *Acta Obstet Gynecol Scand* 2006;85(11):1327-30. PMID: 17091412. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
229. North RA, McCowan LM, Dekker GA, et al. Clinical risk prediction for pre-eclampsia in nulliparous women: development of model in international prospective cohort. *BMJ* 2011;342:d1875. PMID: 21474517. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
230. O'Gorman N, Wright D, Syngelaki A, et al. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. *Am J Obstet Gynecol* 2015 Aug 18 PMID: 26297382. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
231. Odegard RA, Vatten LJ, Nilsen ST, et al. Risk factors and clinical manifestations of pre-eclampsia. *BJOG* 2000 Nov;107(11):1410-6. PMID: 11117771. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
232. Odibo AO, Zhong Y, Goetzinger KR, et al. First-trimester placental protein 13, PAPP-A, uterine artery Doppler and maternal characteristics in the prediction of pre-eclampsia. *Placenta* 2011 Aug;32(8):598-602. PMID: 21652068. **KQ1E12, KQ1aE12, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
233. Ohkuchi A, Iwasaki R, Ojima T, et al. Increase in systolic blood pressure of > or = 30 mm Hg and/or diastolic blood pressure of > or = 15 mm Hg during pregnancy: is it pathologic? *Hypertens Pregnancy* 2003;22(3):275-85. PMID: 14572364. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**

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234. Oliveira N, Magder LS, Blitzer MG, et al. First Trimester Prediction of Preeclampsia: External validity of algorithms in a prospectively enrolled cohort. *Ultrasound Obstet Gynecol* 2014 Jun 10;44(3):279-85. PMID: 24913190. **KQ1E12, KQ1aE12, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
235. Oliveira N, Doyle LE, Atlas RO, et al. External validity of first trimester algorithms in the prediction of pre-eclampsia disease severity. *Ultrasound Obstet Gynecol* 2014 Jun 10;44(3):286-92. PMID: 24912952. **KQ1E12, KQ1aE12, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
236. Oliveira SM, Arcuri EA, Santos JL. Cuff width influence on blood pressure measurement during the pregnant-puerperal cycle. *J Adv Nurs* 2002 Apr;38(2):180-9. PMID: 11940131. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
237. Oloyede OA, Iketubosin F. Uterine artery Doppler study in second trimester of pregnancy. *Pan Afr Med J* 2013;15:87. PMID: None. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
238. Onwudiwe N, Yu CK, Poon LC, et al. Prediction of pre-eclampsia by a combination of maternal history, uterine artery Doppler and mean arterial pressure. *Ultrasound Obstet Gynecol* 2008 Dec;32(7):877-83. PMID: 18991324. **KQ1E12, KQ1aE12, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
239. Osman O, Bakare AO, Elamin S. The prevalence of proteinuria among pregnant women as detected by a semi-quantitative method: a single center experience. *Arab J Nephrol Transplant* 2011 May;4(2):77-82. PMID: 21999855. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
240. Osmundson SS, Lafayette RA, Bowen RA, et al. Maternal proteinuria in twin compared with singleton pregnancies. *Obstet Gynecol* 2014 Aug;124(2:Pt 1):t-7. PMID: 25004349. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
241. Ozcan T, Kaleli B, Ozeren M, et al. Urinary calcium to creatinine ratio for predicting preeclampsia. *Am J Perinatol* 1995 Sep;12(5):349-51. PMID: 8540941. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
242. Palomaki GE, Haddow JE, Haddow HR, et al. Modeling risk for severe adverse outcomes using angiogenic factor measurements in women with suspected preterm preeclampsia. *Prenat Diagn* 2015 Jan 6;35(4):386-93. PMID: 25641027. **KQ1E12, KQ1aE12, KQ2E3, KQ3E3, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
243. Palomaki GE, Haddow JE, Haddow H, et al. [24-OR]: Modeling risk for adverse outcomes in women with suspected preterm preeclampsia using angiogenic factor measurements. *Pregnancy Hypertens* 2015 Jan;5(1):12. PMID: 25787375. **KQ1E12, KQ1aE12, KQ2E6, KQ3E6, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
244. Panella M, Rocchi MC, Landolina C, et al. Blood pressure peaks correlated with plasma fibronectin levels and microalbuminuria in hypertensive pregnancies. *Clin Exp Obstet Gynecol* 1997;24(2):82-5. PMID: 9342469. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
245. Papageorgiou AT, Yu CK, Erasmus IE, et al. Assessment of risk for the development of pre-eclampsia by maternal characteristics and uterine artery Doppler. *BJOG* 2005 Jun;112(6):703-9. PMID: 15924523. **KQ1E3, KQ1aE3, KQ2E3, KQ3E3, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
246. Parazzini F, Bortolus R, Chatenoud L, et al. Risk factors for pregnancy-induced hypertension in women at high risk for the condition. Italian Study of Aspirin in Pregnancy Group. *Epidemiology* 1996 May;7(3):306-8. PMID: 8728447. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**

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247. Park F, Russo K, Williams P, et al. Prediction and prevention of early onset pre-eclampsia: The impact of aspirin after first trimester screening. *Ultrasound Obstet Gynecol* 2015 Feb 11 PMID: 25678383. **KQ1E12, KQ1aE12, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
248. Park FJ, Leung CH, Poon LC, et al. Clinical evaluation of a first trimester algorithm predicting the risk of hypertensive disease of pregnancy. *Aust N Z J Obstet Gynaecol* 2013 Dec;53(6):532-9. PMID: 23919594. **KQ1E12, KQ1aE12, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
249. Park JH, Chung D, Cho HY, et al. Random urine protein/creatinine ratio readily predicts proteinuria in preeclampsia. *Obstet Gynecol Sci* 2013 Jan;56(1):8-14. PMID: 24327974. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
250. Parra-Cordero M, Rodrigo R, Barja P, et al. Prediction of early and late pre-eclampsia from maternal characteristics, uterine artery Doppler and markers of vasculogenesis during first trimester of pregnancy. *Ultrasound Obstet Gynecol* 2013 May;41(5):538-44. PMID: 22807133. **KQ1E12, KQ1aE12, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
251. Parra-Cordero M, Sepulveda-Martinez A, Preisler J, et al. Role of the Glucose Tolerance Test as a Predictor of Preeclampsia. *Gynecol Obstet Invest* 2014 Jun 5 PMID: 24903217. **KQ1E3, KQ1aE3, KQ2E3, KQ3E3, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
252. Paruk F, Moodley J, Daya PK, et al. Screening for proteinuria in hypertensive disorders of pregnancy. *J Obstet Gynaecol* 1997 Nov;17(6):528-30. PMID: 15511949. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
253. Paternoster DM, Stella A, Mussap M, et al. Predictive markers of pre-eclampsia in hypertensive disorders of pregnancy. *Int J Gynaecol Obstet* 1999 Sep;66(3):237-43. PMID: 10580670. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E6, KQ4aE7, KQ4bE6, KQ4cE4, KQ5E4.**
254. Payne B, Magee LA, Cote AM, et al. PIERS proteinuria: relationship with adverse maternal and perinatal outcome. *J Obstet Gynaecol Can* 2011 Jun;33(6):588-97. PMID: 21846448. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E4, KQ4aE2, KQ4bE4, KQ4cE4, KQ5E6.**
255. Peek M, Shennan A, Halligan A, et al. Hypertension in pregnancy: which method of blood pressure measurement is most predictive of outcome? *Obstet Gynecol* 1996 Dec;88(6):1030-3. PMID: 8942848. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
256. Penny JA, Halligan AW, Shennan AH, et al. Automated, ambulatory, or conventional blood pressure measurement in pregnancy: which is the better predictor of severe hypertension? *Am J Obstet Gynecol* 1998 Mar;178(3):521-6. PMID: 9539520. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE4, KQ4bE3, KQ4cE4, KQ5E4.**
257. Phaloprakarn C, Tangjitgamol S. Risk assessment for preeclampsia in women with gestational diabetes mellitus. *J Perinat Med* 2009;37(6):617-21. PMID: 19591558. **KQ1E1, KQ1aE1, KQ2E1, KQ3E1, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
258. Phelan LK, Brown MA, Davis GK, et al. A prospective study of the impact of automated dipstick urinalysis on the diagnosis of preeclampsia. *Hypertens Pregnancy* 2004;23(2):135-42. PMID: 15369647. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE7, KQ4bE3, KQ4cE3, KQ5E3.**
259. Phuapradit W, Manusook S, Lolekha P. Urinary calcium/creatinine ratio in the prediction of preeclampsia. *Aust N Z J Obstet Gynaecol* 1993 Aug;33(3):280-1. PMID: 8304893. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
260. Plasencia W, Maiz N, Bonino S, et al. Uterine artery Doppler at 11 + 0 to 13 + 6 weeks in the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol* 2007 Oct;30(5):742-9. PMID: 17899573. **KQ1E12, KQ1aE12, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**

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261. Plasencia W, Maiz N, Poon L, et al. Uterine artery Doppler at 11 + 0 to 13 + 6 weeks and 21 + 0 to 24 + 6 weeks in the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol* 2008 Aug;32(2):138-46. PMID: 18634131. **KQ1E12, KQ1aE12, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
262. Pomini F, Scavo M, Ferrazzani S, et al. There is poor agreement between manual auscultatory and automated oscillometric methods for the measurement of blood pressure in normotensive pregnant women. *J Matern Fetal Med* 2001 Dec;10(6):398-403. PMID: 11798450. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
263. Poon LC, Kametas N, Bonino S, et al. Urine albumin concentration and albumin-to-creatinine ratio at 11(+0) to 13(+6) weeks in the prediction of pre-eclampsia. *BJOG* 2008 Jun;115(7):866-73. PMID: 18485165. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
264. Poon LC, Karagiannis G, Leal A, et al. Hypertensive disorders in pregnancy: screening by uterine artery Doppler imaging and blood pressure at 11-13 weeks. *Ultrasound Obstet Gynecol* 2009 Nov;34(5):497-502. PMID: 19827052. **KQ1E12, KQ1aE12, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
265. Poon LC, Kametas NA, Maiz N, et al. First-trimester prediction of hypertensive disorders in pregnancy. *Hypertension* 2009 May;53(5):812-8. PMID: 19273739. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
266. Poon LC, Kametas NA, Chelemen T, et al. Maternal risk factors for hypertensive disorders in pregnancy: a multivariate approach. *J Hum Hypertens* 2010 Feb;24(2):104-10. PMID: 19516271. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
267. Poon LC, Stratieva V, Piras S, et al. Hypertensive disorders in pregnancy: combined screening by uterine artery Doppler, blood pressure and serum PAPP-A at 11-13 weeks. *Prenat Diagn* 2010 Mar;30(3):216-23. PMID: 20108221. **KQ1E12, KQ1aE12, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
268. Poon LC, Kametas NA, Valencia C, et al. Hypertensive disorders in pregnancy: screening by systolic diastolic and mean arterial pressure at 11-13 weeks. *Hypertens Pregnancy* 2011;30(1):93-107. PMID: 20818956. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
269. Poon LC, Syngelaki A, Akolekar R, et al. Combined screening for preeclampsia and small for gestational age at 11-13 weeks. *Fetal Diagn Ther* 2013;33(1):16-27. PMID: 22986844. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
270. Poon LC, Nicolaides KH. Early prediction of preeclampsia. *Obstet Gynecol Int* 2014;2014:297397. PMID: 25136369. **KQ1E3, KQ1aE3, KQ2E3, KQ3E3, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
271. Poon LCY, Maiz N, Valencia C, et al. First-trimester maternal serum pregnancy-associated plasma protein-A and pre-eclampsia. *Ultrasound Obstet Gynecol* 2009;33(1):23-33. PMID: 19090499. **KQ1E12, KQ1aE12, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
272. Porter KB, O'Brien WF, Kiefert V, et al. Finapres: a noninvasive device to monitor blood pressure. *Obstet Gynecol* 1991 Sep;78(3:Pt 1):t-3. PMID: 1876379. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
273. Quinn M. Automated blood pressure measurement devices: a potential source of morbidity in preeclampsia? *Am J Obstet Gynecol* 1994 May;170(5:Pt 1):t-7. PMID: 8178857. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**

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274. Ramirez Avila GM, Gapelyuk A, Marwan N, et al. Classification of cardiovascular time series based on different coupling structures using recurrence networks analysis. *Philos Transact Ser A Math Phys Eng Sci* 2013 Aug 28;371(1997):20110623. PMID: 23858486. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
275. Rang S, Wolf H, van Montfrans GA, et al. Serial assessment of cardiovascular control shows early signs of developing pre-eclampsia. *J Hypertens* 2004 Feb;22(2):369-76. PMID: 15076196. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
276. Rang S, van Montfrans GA, Wolf H. Serial hemodynamic measurement in normal pregnancy, preeclampsia, and intrauterine growth restriction. *Am J Obstet Gynecol* 2008 May;198(5):519. PMID: 18279824. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
277. Rani SS, Ghalaut V, Lata S, et al. Correlation of 2 hour, 4 hour, 8 hour and 12 hour urine protein with 24 hour urinary protein in preeclampsia. *J Family Reprod Health* 2014 Sep;8(3):131-4. PMID: 25628723. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
278. Raniolo E, Phillipou G. Prediction of pregnancy-induced hypertension by means of the urinary calcium:creatinine ratio. *Med J Aust* 1993 Jan 18;158(2):98-100. PMID: 8419785. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
279. Reinders A, Cuckson AC, Jones CR, et al. Validation of the Welch Allyn 'Vital Signs' blood pressure measurement device in pregnancy and pre-eclampsia. *BJOG* 2003 Feb;110(2):134-8. PMID: 12618156. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
280. Reinders A, Cuckson AC, Lee JT, et al. An accurate automated blood pressure device for use in pregnancy and pre-eclampsia: the Microlife 3BTO-A. *BJOG* 2005 Jul;112(7):915-20. PMID: 15957992. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
281. Reinders LW, Mos CN, Thornton C, et al. Time poor: rushing decreases the accuracy and reliability of blood pressure measurement technique in pregnancy. *Hypertens Pregnancy* 2006;25(2):81-91. PMID: 16867915. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
282. Rey E, Pilon F, Boudreault J. Home blood pressure levels in pregnant women with chronic hypertension. *Hypertens Pregnancy* 2007;26(4):403-14. PMID: 18066959. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
283. Rey E, Morin F, Boudreault J, et al. Blood pressure assessments in different subtypes of hypertensive pregnant women: office versus home patient- or nurse-measured blood pressure. *Hypertens Pregnancy* 2009 May;28(2):168-77. PMID: 19437227. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
284. Rhode MA, Shapiro H, Jones OW, III. Indicated vs. routine prenatal urine chemical reagent strip testing. *J Reprod Med* 2007 Mar;52(3):214-9. PMID: 17465289. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4.**
285. Risberg A, Larsson A, Olsson K, et al. Relationship between urinary albumin and albumin/creatinine ratio during normal pregnancy and pre-eclampsia. *Scan J Clin Lab Invest* 2004;64(1):17-23. PMID: 15025425. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4aE6, KQ4bE6, KQ4cE4, KQ5E4.**
286. Rizk DE, Agarwal MM, Pathan JY, et al. Predicting proteinuria in hypertensive pregnancies with urinary protein-creatinine or calcium-creatinine ratio. *J Perinatol* 2007 May;27(5):272-7. PMID: 17453039. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
287. Robert M, Sepandj F, Liston RM, et al. Random protein-creatinine ratio for the quantitation of proteinuria in pregnancy. *Obstet Gynecol* 1997 Dec;90(6):893-5. PMID: 9397097. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE10, KQ4bE2, KQ4cE2, KQ5E2.**

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288. Rodrigue CZ, Jr., Weyer KL, Dornelles A, et al. Comparison of timed urine collection to protein-creatinine ratio for the diagnosis of preeclampsia. *Obstet Gynecol* 2014 May;123(Suppl):76s-7S. PMID: 24770270. **KQ1E11, KQ1aE11, KQ2E11, KQ3E11, KQ4E11, KQ4aE11, KQ4bE11, KQ4cE11, KQ5E11.**
289. Rodriguez-Thompson D, Lieberman ES. Use of a random urinary protein-to-creatinine ratio for the diagnosis of significant proteinuria during pregnancy. *Am J Obstet Gynecol* 2001 Oct;185(4):808-11. PMID: 11641656. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4aE6, KQ4bE4, KQ4cE4, KQ5E4.**
290. Rogers CJ, Hewison J, Tsigas E. [236-POS]: Patient perspectives on screening/diagnostic tests, clinical trials, and expectant management for preeclampsia. *Pregnancy Hypertens* 2015 Jan;5(1):119. PMID: 25787586. **KQ1E11, KQ1aE11, KQ2E11, KQ3E11, KQ4E11, KQ4aE11, KQ4bE11, KQ4cE11, KQ5E11.**
291. Ros HS, Cnattingius S, Lipworth L. Comparison of risk factors for preeclampsia and gestational hypertension in a population-based cohort study. *Am J Epidemiol* 1998 Jun 1;147(11):1062-70. PMID: 9620050. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
292. Ross-McGill H, Hewison J, Hirst J, et al. Antenatal home blood pressure monitoring: a pilot randomised controlled trial. *BJOG* 2000 Feb 1;107(2):217-21. PMID: 10688505. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
293. Rylander R, Bullarbo M. [162-POS] : Blood pressure criteria for the detection of preeclampsia. *Pregnancy Hypertens* 2015 Jan;5(1):84. PMID: 25787513. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
294. Saftlas AF, Olson DR, Franks AL, et al. Epidemiology of preeclampsia and eclampsia in the United States, 1979-1986. *Am J Obstet Gynecol* 1990 Aug;163(2):460-5. PMID: 2386132. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
295. Sarno L, Maruotti GM, Saccone G, et al. Pregnancy outcome in proteinuria-onset and hypertension-onset preeclampsia. *Hypertens Pregnancy* 2015 Mar 23;34(3):284-90. PMID: 25799185. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
296. Saudan PJ, Brown MA, Farrell T, et al. Improved methods of assessing proteinuria in hypertensive pregnancy. *Br J Obstet Gynaecol* 1997 Oct;104(10):1159-64. PMID: 9332994. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4aE10, KQ4bE2, KQ4cE4, KQ5E4.**
297. Saudan PJ, Farrell TJ, Brown MA. Beta2-microglobulin in hypertensive pregnancies. *Am J Kidney Dis* 1998 Feb;31(2):308-12. PMID: 9469502. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
298. Savitz DA, Zhang J. Pregnancy-induced hypertension in North Carolina, 1988 and 1989. *Am J Public Health* 1992 May;82(5):675-9. PMID: 1566945. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
299. Saxena I, Kapoor S, Gupta RC. Detection of proteinuria in pregnancy: comparison of qualitative tests for proteins and dipsticks with urinary protein creatinine index. *J Clin Diagn Res* 2013 Sep;7(9):1846-8. PMID: 24179878. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
300. Scazzocchio E, Figueras F, Crispi F, et al. Performance of a first-trimester screening of preeclampsia in a routine care low-risk setting. *Am J Obstet Gynecol* 2013 Mar;208(3):203. PMID: 23246313. **KQ1E12, KQ1aE12, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
301. Schenone MH, Miller D, Samson JE, et al. Eclampsia characteristics and outcomes: a comparison of two eras. *J Pregnancy* 2013;2013:826045. PMID: 23691323. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**

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302. Schneider S, Freerksen N, Maul H, et al. Risk groups and maternal-neonatal complications of preeclampsia--current results from the national German Perinatal Quality Registry. *J Perinat Med* 2011 May;39(3):257-65. PMID: 21309631. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
303. Schubert FP, Abernathy MP. Alternate evaluations of proteinuria in the gravid hypertensive patient. *J Reprod Med* 2006 Sep;51(9):709-14. PMID: 17039700. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE10, KQ4bE2, KQ4cE2, KQ5E2.**
304. Schwartz WJ, III, Rayburn WF, Turnbull GL, et al. Blood pressure monitoring during pregnancy. Accuracy of portable devices designed for obese patients. *J Reprod Med* 1996 Aug;41(8):581-5. PMID: 8866385. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
305. Seed PT, Chappell LC, Black MA, et al. Prediction of preeclampsia and delivery of small for gestational age babies based on a combination of clinical risk factors in high-risk women. *Hypertens Pregnancy* 2011;30(1):58-73. PMID: 20795821. **KQ1E12, KQ1aE12, KQ2E2, KQ3E2, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
306. Seong WJ, Chong GO, Hong DG, et al. Clinical significance of serum albumin level in pregnancy-related hypertension. *J Obstet Gynaecol Res* 2010 Dec;36(6):1165-73. PMID: 21040199. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
307. Seow KM, Tang MH, Chuang J, et al. The correlation between renal function and systolic or diastolic blood pressure in severe preeclamptic women. *Hypertens Pregnancy* 2005;24(3):247-57. PMID: 16263597. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
308. Sep SJ, Smits LJ, Prins MH, et al. Simple prepregnant prediction rule for recurrent early-onset hypertensive disease in pregnancy. *Reprod Sci* 2009 Jan;16(1):80-7. PMID: 19144890. **KQ1E2, KQ1aE2, KQ2E2, KQ3E2, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
309. Sethuram R, Kiran TS, Weerakkody AN. Is the urine spot protein/creatinine ratio a valid diagnostic test for pre-eclampsia? *J Obstet Gynaecol* 2011;31(2):128-30. PMID: 21281026. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4bE4, KQ4cE4, KQ5E4.**
310. Shaarawy M, Salem ME. The clinical value of microtransferrinuria and microalbuminuria in the prediction of pre-eclampsia. *Clin Chem Lab Med* 2001 Jan;39(1):29-34. PMID: 11256797. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
311. Shennan A, Halligan A, Gupta M, et al. Oscillometric blood pressure measurements in severe pre-eclampsia: validation of the SpaceLabs 90207. *Br J Obstet Gynaecol* 1996 Feb;103(2):171-3. PMID: 8616136. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
312. Shennan A, Gupta M, Halligan A, et al. Lack of reproducibility in pregnancy of Korotkoff phase IV as measured by mercury sphygmomanometry. *Lancet* 1996 Jan 20;347(8995):139-42. PMID: 8544546. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
313. Shennan AH, Kissane J, de SM. Validation of the SpaceLabs 90207 ambulatory blood pressure monitor for use in pregnancy. *Br J Obstet Gynaecol* 1993 Oct;100(10):904-8. PMID: 8217971. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
314. Sibai BM, Gordon T, Thom E, et al. Risk factors for preeclampsia in healthy nulliparous women: a prospective multicenter study. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *Am J Obstet Gynecol* 1995 Feb;172(2 Pt 1):642-8. PMID: 7856699. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
315. Sibai BM, Ewell M, Levine RJ, et al. Risk factors associated with preeclampsia in healthy nulliparous women. The Calcium for Preeclampsia Prevention (CPEP) Study Group. *Am J Obstet Gynecol* 1997 Nov;177(5):1003-10. PMID: 9396883. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**

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317. Simeone S, Lojo C, Garcia-Esteve L, et al. Psychological impact of first-trimester prevention for preeclampsia on anxiety. *Prenat Diagn* 2015 Jan;35(1):60-4. PMID: 25156501. **KQ1E12, KQ1aE12, KQ2E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
318. Simonazzi G, Vicenzi C, Rizzo MA, et al. Prospective evaluation of the risk of pre-eclampsia using logistic regression analysis. *Ultrasound Obstet Gynecol* 2007 Sep;30(3):312-7. PMID: 17688308. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
319. Singh R, Tandon I, Deo S, et al. Does microalbuminuria at mid-pregnancy predict development of subsequent pre-eclampsia? *J Obstet Gynaecol Res* 2013 Feb;39(2):478-83. PMID: 22925380. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
320. Sirohiwal D, Dahiya K, Khaneja N. Use of 24-hour urinary protein and calcium for prediction of preeclampsia. *Taiwan J Obstet Gynecol* 2009 Jun;48(2):113-5. PMID: 19574169. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
321. Skrastad R, Hov G, Blaas HG, et al. Risk assessment for preeclampsia in nulliparous women at 11-13 weeks gestational age: prospective evaluation of two algorithms. *BJOG* 2014 Dec 4 PMID: 25471057. **KQ1E12, KQ1aE12, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
322. Skrastad RB, Hov GG, Blaas HG, et al. A prospective study of screening for hypertensive disorders of pregnancy at 11-13 weeks in a Scandinavian population. *Acta Obstet Gynecol Scand* 2014 Dec;93(12):1238-47. PMID: 25146367. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
323. Smith CV, Selig CL, Rayburn WF, et al. Reliability of compact electronic blood pressure monitors for hypertensive pregnant women. *J Reprod Med* 1990 Apr;35(4):399-401. PMID: 2352232. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
324. Somanathan N, Farrell T, Galimberti A. A comparison between 24-hour and 2-hour urine collection for the determination of proteinuria. *J Obstet Gynaecol* 2003 Jul;23(4):378-80. PMID: 12881076. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
325. Stamilio DM, Sehdev HM, Morgan MA, et al. Can antenatal clinical and biochemical markers predict the development of severe preeclampsia? *Am J Obstet Gynecol* 2000 Mar;182(3):589-94. PMID: 10739512. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
326. Stone JL, Lockwood CJ, Berkowitz GS, et al. Risk factors for severe preeclampsia. *Obstet Gynecol* 1994 Mar;83(3):357-61. PMID: 8127525. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
327. Stout MJ, Scifres CM, Stamilio DM. Diagnostic utility of urine protein-to-creatinine ratio for identifying proteinuria in pregnancy. *J Matern Fetal Neonatal Med* 2013 Jan;26(1):66-70. PMID: 23020712. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4bE4, KQ4cE4, KQ5E4.**
328. Sukur YE, Yalcin I, Kahraman K, et al. Predictive value of 3+ spot urinary protein value measured by dipstick in hypertensive pregnant patients. *Hypertens Pregnancy* 2013 May;32(2):139-45. PMID: 23725079. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
329. Taherian AA, Dehbashi S, Baghban M. The relationship between random urinary protein-to-creatinine ratio and 24-hour urine protein in diagnosis of proteinuria in mild preeclampsia. *J Res Med Sci* 2006;11(1):6-12. PMID: None. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**

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330. Takahashi K, Ohkuchi A, Suzuki H, et al. Biophysical interaction between blood pressure and uterine artery Doppler for the occurrence of early-onset preeclampsia: A prospective cohort study. *Pregnancy Hypertens* 2013 Oct;3(4):270-7. PMID: 26103807. **KQ1E12, KQ1aE12, KQ2E3, KQ3E3, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
331. Tape TG, Rayburn WF, Bremer KD, et al. Ambulatory blood pressure monitoring during pregnancy with a new, small, easily concealed monitor. *J Reprod Med* 1994 Dec;39(12):968-72. PMID: 7884755. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
332. Taylor RS, Gamble G, McCowan L, et al. Sleep effects on ambulatory blood pressure measurements in pregnant women. *Am J Hypertens* 2001 Jan;14(1):38-43. PMID: 11206677. **KQ1E6, KQ1aE6, KQ2E12, KQ3E12, KQ4E6, KQ4aE6, KQ4bE6, KQ4cE6, KQ5E6.**
333. Thornton CE, Makris A, Ogle RF, et al. Role of proteinuria in defining pre-eclampsia: clinical outcomes for women and babies. *Clin Exp Pharmacol Physiol* 2010 Apr;37(4):466-70. PMID: 19930427. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE2, KQ4bE2, KQ4cE2, KQ5E2.**
334. Tomoda S, Tamura T, Kitanaka T, et al. First trimester biological markers for the prediction of pregnancy-induced hypertension. *Am J Perinatol* 1996 Feb;13(2):89-93. PMID: 8672192. **KQ1E12, KQ1aE12, KQ2E4, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
335. Tranquilli AL, Giannubilo SR, Dell'Uomo B, et al. Prediction of gestational hypertension or intrauterine fetal growth restriction by mid-trimester 24-h ambulatory blood pressure monitoring. *Int J Gynaecol Obstet* 2004 May;85(2):126-31. PMID: 15099773. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
336. Tucker JS, Hall MH, Howie PW, et al. Should obstetricians see women with normal pregnancies? A multicentre randomised controlled trial of routine antenatal care by general practitioners and midwives compared with shared care led by obstetricians. *BMJ* 1996;312:554-9. PMID: 8595287. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
337. Tun C, Quinones JN, Kurt A, et al. Comparison of 12-hour urine protein and protein:creatinine ratio with 24-hour urine protein for the diagnosis of preeclampsia. *Am J Obstet Gynecol* 2012 Sep;207(3):233-8. PMID: 22939731. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4bE2, KQ4cE2, KQ5E2.**
338. Ukah UV. [247-POS]: Preliminary external validation of the fullPIERS risk prediction model for women with pre-eclampsia using the miniPIERS dataset. *Pregnancy Hypertens* 2015 Jan;5(1):124-5. PMID: 25787597. **KQ1E12, KQ1aE12, KQ2E6, KQ3E6, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
339. Uyar I, Kurt S, Demirtas O, et al. The value of uterine artery Doppler and NT-proBNP levels in the second trimester to predict preeclampsia. *Arch Gynecol Obstet* 2014 Dec 6;291(6):1253-8. PMID: 25480410. **KQ1E12, KQ1aE12, KQ2E3, KQ3E3, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
340. Vahdat M, Kashanian M, Sariri E, et al. Evaluation of the value of calcium to creatinine ratio for predicting of pre-eclampsia. *J Matern Fetal Neonatal Med* 2012 Dec;25(12):2793-4. PMID: 22866874. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
341. Valdes E, Sepulveda-Martinez A, Tong A, et al. Assessment of protein:creatinine ratio versus 24-hour urine protein in the diagnosis of preeclampsia. *Gynecol Obstet Invest* 2015 Jun 3 PMID: 26045043. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4bE4, KQ4cE4, KQ5E12.**

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342. van Kuijk SM, Nijdam ME, Janssen KJ, et al. A model for preconceptional prediction of recurrent early-onset preeclampsia: derivation and internal validation. *Reprod Sci* 2011 Nov;18(11):1154-9. PMID: 21673281. **KQ1E3, KQ1aE3, KQ2E2, KQ3E2, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
343. Verdonk K, Niemeijer I, Hop W, et al. Variation of urinary protein to creatinine ratio during the day in women with suspected pre-eclampsia. *BJOG* 2014 Apr 25;121(13):1660-5. PMID: 24762212. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4bE4, KQ4cE2, KQ5E2.**
344. Verghese L, Alam S, Beski S, et al. Antenatal screening for pre-eclampsia: evaluation of the NICE and pre-eclampsia community guidelines. *J Obstet Gynaecol* 2012 Feb;32(2):128-31. PMID: 22296420. **KQ1E3, KQ1aE3, KQ2E3, KQ3E3, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
345. Verlohren S. Re: Longitudinal changes in maternal soluble endoglin and angiotensin-2 in women at risk for pre-eclampsia. A. Khalil, N. Maiz, R. Garcia-Mandujano, M. Elkhoul and K. H. Nicolaidis. *Ultrasound Obstet Gynecol* 2014; 44: 402-410. *Ultrasound Obstet Gynecol* 2014 Oct;44(4):386. PMID: 25274543. **KQ1E3, KQ1aE3, KQ2E3, KQ3E3, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
346. Villar J, Ba'aqeel H, Piaggio G, et al. Who antenatal care randomised trial for the evaluation of a new model of routine antenatal care. *Lancet* 2001;357(9268):1551-64. PMID: 11377642. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
347. Villar J, Carroli G, Wojdyla D, et al. Preeclampsia, gestational hypertension and intrauterine growth restriction, related or independent conditions? *Am J Obstet Gynecol* 2006 Apr;194(4):921-31. PMID: 16580277. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
348. Vollebregt KC, Gisolf J, Guelen I, et al. Limited accuracy of the hyperbaric index, ambulatory blood pressure and sphygmomanometry measurements in predicting gestational hypertension and preeclampsia. *J Hypertens* 2010 Jan;28(1):127-34. PMID: 19770679. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
349. Vollebregt KC, Boer K, van der Post JA, et al. Association of three different techniques to measure blood pressure in the first trimester with the development of hypertensive disorders of pregnancy. *Acta Obstet Gynecol Scand* 2013 Jan;92(1):53-60. PMID: 22881432. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
350. Vreeburg SA, Jacobs DJ, Dekker GA, et al. Hypertension during pregnancy in South Australia, part 2: risk factors for adverse maternal and/or perinatal outcome - results of multivariable analysis. *Aust N Z J Obstet Gynaecol* 2004 Oct;44(5):410-8. PMID: 15387861. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
351. Walker SP, Permezel M, Brennecke SP, et al. Blood pressure in late pregnancy and work outside the home. *Obstet Gynecol* 2001 Mar;97(3):361-5. PMID: 11239637. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
352. Wang T, Zhou R, Gao L, et al. Elevation of Urinary Adipsin in Preeclampsia: Correlation With Urine Protein Concentration and the Potential Use for a Rapid Diagnostic Test. *Hypertension* 2014 Jun 23;64(4):846-51. PMID: 24958499. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
353. Waterstone M, Bewley S, Wolfe C. Incidence and predictors of severe obstetric morbidity: case-control study. *BMJ* 2001 May 5;322(7294):1089-93. PMID: 11337436. **KQ1E12, KQ1aE12, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**

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354. Waugh J, Bell SC, Kilby M, et al. Effect of concentration and biochemical assay on the accuracy of urine dipsticks in hypertensive pregnancies. *Hypertens Pregnancy* 2001;20(2):205-17. PMID: 12044331. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4bE4, KQ4cE4, KQ5E4.**
355. Waugh J, Kilby M, Lambert P, et al. Validation of the DCA 2000 microalbumin:creatinine ratio urinalyzer for its use in pregnancy and preeclampsia. *Hypertens Pregnancy* 2003;22(1):77-92. PMID: 12648445. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4aE3, KQ4bE2, KQ4cE2, KQ5E2.**
356. Waugh J, Bell SC, Kilby MD, et al. Urinary microalbumin/creatinine ratios: reference range in uncomplicated pregnancy. *Clin Sci (Lond)* 2003 Feb;104(2):103-7. PMID: 12546632. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
357. Waugh J, Habiba MA, Bosio P, et al. Patient initiated home blood pressure recordings are accurate in hypertensive pregnant women. *Hypertens Pregnancy* 2003;22(1):93-7. PMID: 12648446. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
358. Waugh J, Bell SC, Kilby MD, et al. Urine protein estimation in hypertensive pregnancy: which thresholds and laboratory assay best predict clinical outcome? *Hypertens Pregnancy* 2005;24(3):291-302. PMID: 16263601. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
359. Waugh JJ, Halligan AW, Shennan AH. Ambulatory monitoring and self-monitoring of blood pressure during pregnancy. *Blood Press Monit* 2000 Feb;5(1):3-10. PMID: 10804445. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**
360. Waugh JJ, Bell SC, Kilby MD, et al. Optimal bedside urinalysis for the detection of proteinuria in hypertensive pregnancy: a study of diagnostic accuracy. *BJOG* 2005 Apr;112(4):412-7. PMID: 15777437. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E4, KQ4bE4, KQ4cE4, KQ5E4.**
361. Wen SW, Kramer MS, Hoey J, et al. Terminal digit preference, random error, and bias in routine clinical measurement of blood pressure. *J Clin Epidemiol* 1993 Oct;46(10):1187-93. PMID: 8410103. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
362. Wheeler TL, Blackhurst DW, Dellinger EH, et al. Usage of spot urine protein to creatinine ratios in the evaluation of preeclampsia. *Am J Obstet Gynecol* 2007 May;196(5):465-4. PMID: 17466704. **KQ1E2, KQ1aE2, KQ2E12, KQ3E12, KQ4E2, KQ4bE2, KQ4cE2, KQ5E2.**
363. Widmer M, Cuesta CB, Khan K, et al. [93-OR]: Accuracy of angiogenic biomarkers for predicting preeclampsia: An observational study. *Pregnancy Hypertens* 2015 Jan;5(1):50. PMID: 25787319. **KQ1E12, KQ1aE12, KQ2E6, KQ3E6, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
364. Witlin AG, Saade GR, Mattar F, et al. Risk factors for abruptio placentae and eclampsia: analysis of 445 consecutively managed women with severe preeclampsia and eclampsia. *Am J Obstet Gynecol* 1999 Jun;180(6:Pt 1):t-9. PMID: 10368466. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
365. Wiwanitkit V. Periodic urinary protein creatinine ratio for predicting significant proteinuria in preeclampsia in different alternatives: time effectiveness analysis. *Arch Gynecol Obstet* 2010 Mar;281(3):571-3. PMID: 19568760. **KQ1E1, KQ1aE1, KQ2E12, KQ3E12, KQ4E1, KQ4aE1, KQ4bE1, KQ4cE1, KQ5E1.**
366. Woelkers D, Barton J, von DP, et al. [73-OR]: Rates of adverse outcomes are elevated in preterm patients with suspected hypertensive disorders without diagnostic criteria for preeclampsia. *Pregnancy Hypertens* 2015 Jan;5(1):39. PMID: 25787423. **KQ1E3, KQ1aE3, KQ2E12, KQ3E12, KQ4E3, KQ4aE3, KQ4bE3, KQ4cE3, KQ5E3.**

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367. Woelkers D, Barton J, Dadelszen P, et al. [71-OR]: The revised 2013 ACOG definitions of hypertensive disorders of pregnancy significantly increase the diagnostic prevalence of preeclampsia. *Pregnancy Hypertens* 2015 Jan;5(1):38. PMID: 25787421. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE4, KQ4bE4, KQ4cE4, KQ5E4.**
368. Wright D, Akolekar R, Syngelaki A, et al. A competing risks model in early screening for preeclampsia. *Fetal Diagn Ther* 2012;32(3):171-8. PMID: 22846473. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
369. Wright D, Syngelaki A, Akolekar R, et al. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. *Am J Obstet Gynecol* 2015 Feb 25;213(1):62. PMID: 25724400. **KQ1E12, KQ1aE12, KQ2E13, KQ3E4, KQ4E12, KQ4aE12, KQ4bE12, KQ4cE12, KQ5E12.**
370. Yamada T, Kojima T, Akaishi R, et al. Problems in methods for the detection of significant proteinuria in pregnancy. *J Obstet Gynaecol Res* 2014 Jan;40(1):161-6. PMID: 24102664. **KQ1E4, KQ1aE4, KQ2E12, KQ3E12, KQ4E4, KQ4aE10, KQ4bE6, KQ4cE6, KQ5E4.**
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Appendix E. Summary of Methodological Principles Used in Evaluating Risk Prediction Models

1. The source of data for risk prediction models is ideally from cohort, nested case-control or case-cohort studies.⁸³ Prospective cohort data are less prone to missing data and predictors than are retrospective cohort data. RCT and registry databases also are sometimes used for risk prediction model validation, but they are subject to greater risk of bias relative to cohort and nested designs.
2. The size of the study and incidence of preeclampsia determines the number of outcome events available for the model development process.⁸³ For model internal validation, a rule of thumb is that there should be ten events for every predictor in the model. The low prevalence of preterm preeclampsia poses model development challenges. Models developed with this risk of bias are less likely to perform well in external validation.
3. Discrimination and calibration characterize the model performance, and without information on both it is difficult to determine the degree to which a model correctly classifies those who ultimately develop the condition of interest, and to compare models as new predictors are added and removed during model development and validation. As stated in the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies (CHARMS) checklist, the absence of either calibration or discrimination hinders the full appraisal of models.⁸³
4. The discriminatory capacity of predictive tools is often represented with the Area under the Receiver Operator Curve (AUC) which in general terms depicts the degree to which a test correctly classifies those with and without the condition of interest.¹⁹⁵ Values of the AUC range from 0.5 to 1.0, with 0.5 representing discrimination no better than a coin toss and 1.0 representing perfect classification. Guidelines for interpretation of discriminatory power are as follows: AUC values below 0.70 are generally considered as inadequate, from 0.70 to 0.79 as adequate, and 0.80 or higher as good to excellent.⁹² The AUC, or *c* statistic, is the most commonly reported measure of performance, specifically model discrimination, and provides a general basis for evaluating the models we identified. An AUC of at least 0.70 is often cited as the lowest threshold for a clinically useful test.¹⁹⁶
5. Based on the CHARMS checklist, for external validity studies the risk of bias is greater when the research team and setting engaged for the external validation study is independent from the team that developed the model and conducted internal validation.⁸³
6. Models developed following established methods for reducing the risk of bias are more likely to be reproducible in similar populations. Information on differences in the derivation study population and the validation study population is important for interpreting differences in the performance of a model in external validation.⁸⁴ If calibration and discrimination are not upheld in a population with similar characteristics to the model development study, overfitting and risk of bias in the model development process likely account for the lack of reproducibility. When the performance is not upheld in a population with different prevalence of important predictors and the outcome, then a model is not considered transportable – and further adjustments for application in different populations are likely necessary.
7. Clarity in reporting of the risk prediction algorithm and how it would be applied in the clinical setting are important to appraisal of models for potential clinical use recommendations. Clear reporting on the risk algorithm and its calculation, including the necessary variables, coding rules and risk cut-offs are practical requirements for model application.^{83,85}

Appendix F Table 1. Study Design Characteristics of Included Studies (Key Questions 1a, 3, 4a, and 5)

Study and Quality	Study Design	Study Period	Country	Inclusion Criteria	Exclusion Criteria	n	Group
Key Questions 1a and 5							
McDuffie, 1996 ⁹⁷ Fair	RCT	1992-1994 (enrollment)	United States	Healthy women in first trimester of pregnancy who presented for an intake visit	Age <18 or >39 years; completed 13 weeks' gestation; had a past (preterm delivery, preterm labor, abruption placenta, severe PE, classic cesarean delivery, gestational diabetes, incompetent cervix, uterine anomaly, diethylstilbestrol exposure, isoimmunization, >1 2nd-trimester abortion, fetal anomaly, or SGA neonate) or current (multiple gestation, assisted pregnancy, large leiomyoma) high-risk obstetrical condition; had a current medical condition (diabetes, chronic HTN, drug or alcohol abuse, any ongoing medical or psychiatric illness requiring treatment or monitoring); were non-English speaking; or were planning to change insurance carriers during pregnancy	2,764 (randomized)	IG: Schedule of less perinatal visits (9 visits) CG: Routine number of prenatal care visits (14 visits)
Rhode, 2007 ¹¹⁵ Fair	Before-After	November 2000 to March 2004	United States	All pregnant women who enrolled for care and delivered at a hospital-based nursing-midwifery practice between November 2000 and March 2004	Spontaneous abortion, transfer of care, transfer to high-risk care	1,952	IG: Indicated urine testing CG: Routine urine screening
Key Question 3							
Simeone, 2015 ¹⁰² Fair	Prospective cohort study	July 2013 to February 2014 (recruitment)	Spain and Italy	Consecutive women if they had a singleton pregnancy, absence of psychiatric disorder, and low-risk Down syndrome screening (<1/240); high-risk woman matched with the next visited low-risk woman in the 1st trimester screening unit.	NR	255	IG: High-risk women CG: Low-risk women

Appendix F Table 1. Study Design Characteristics of Included Studies (Key Questions 1a, 3, 4a, and 5)

Study and Quality	Study Design	Study Period	Country	Inclusion Criteria	Exclusion Criteria	n	Group
Key Question 4a (sorted by type of test)							
<i>Protein:creatinine spot urine tests</i>							
Tun, 2012 ¹¹⁰ Fair	Diagnostic accuracy	July 1, 2010 to December 31, 2011	United States	Pregnant women ages 18-55 years, >20 weeks' gestation who were admitted to the Lehigh Valley Health Network antepartum unit, undergoing 24-hour urine collection for diagnosis and/or management of PE	Prepregnancy renal disease (24-hour urine protein \geq 300 mg), clinical indication for delivery at time of admission, outside maternal or gestational age range, did not speak English, did not give informed consent, or had been enrolled previously in the study	90	P/Cr spot test
Stout, 2013 ¹⁰⁹ Fair	Diagnostic accuracy	2005-2007	United States	Pregnant women after 20 weeks' gestation who underwent evaluation for suspected PE	Proteinuria (i.e., \geq 300 mg in 24 hours) before 20 weeks' gestation	356	P/Cr spot ratio
Wheeler, 2007 ¹¹³ Fair	Diagnostic accuracy	December 2000 to July 2002	United States	Pregnant women admitted to the Greenville Hospital System University Medical Center for evaluation of preeclampsia, which was, in general, new-onset persistent HTN, worsening HTN, or proteinuria; new-onset HTN was SBP >140 mm Hg or DBP >90 mm Hg after 20 weeks' gestation in a previously normotensive patient, whereas worsening HTN was an increase in BP from baseline taken before 20 weeks' gestation	Women who had bacteriuria on microscopy or who were on more than 24 hours' bed rest, because of a potential poor correlation between spot P/Cr and 24-hour urine collections for protein after prolonged recumbency	126	P/Cr spot ratio
Young, 1996 ¹¹⁴ Fair	Diagnostic accuracy	June 1992-June 1993; December 1993-August 1994	United States	Ambulatory women suspected of having PIH (BP >140/90 mm Hg, SBP >30 mm Hg above baseline or DBP 15 mm Hg above baseline)	Previously diagnosed as having PIH and had been placed on long-term bed rest at home or strict bed rest in the hospital for more than 36 hours	45	P/Cr spot test
Kyle, 2008 ¹⁰⁶ Fair	Diagnostic accuracy	NR	New Zealand	Pregnant women attending a high-risk obstetric medical antenatal clinic if they had automated dipstick analysis of \geq 1+ of new-onset proteinuria on a midstream urine specimen; group of negative or trace proteinuria women on automated dipstick also	Positive urine culture for UTI, underlying proteinuric renal disease, those w/ diabetes w/ an abnormal albumin/Cr in the first trimester.	150	P/Cr spot test

Appendix F Table 1. Study Design Characteristics of Included Studies (Key Questions 1a, 3, 4a, and 5)

Study and Quality	Study Design	Study Period	Country	Inclusion Criteria	Exclusion Criteria	n	Group
				recruited; women attending clinic included those with pre-existing HTN, preexisting DM, gestational DM, renal disease, connective tissue disorders, and other high-risk obstetric and fetal conditions.			
Sethuram, 2011 ¹⁰⁸ Fair	Diagnostic accuracy	January-September 2007	United Kingdom	Women >24 weeks' gestation undergoing evaluation for PE (BP >140/90 mm Hg and urine protein >1+ on dipstick); women with secondary PE to HTN or GDM also included	UTI, renal pathologies, delivered before they could complete their 24-hour urine collection	32	P/Cr spot test
Bhide, 2015 ¹⁰³ Fair	Diagnostic accuracy	NR	United Kingdom	Pregnant women with suspected PE (SBP ≥140 mm Hg and/or DBP ≥90 mm Hg in the antenatal clinic or in the community when checked by midwives or doctors and a spot urine dipstick proteinuria of ≥1+)	>72 hours between starting the 24-hour urine collection and taking the spot P/Cr ratio sample; 24-hour urinary Cr excretion <97 μM/kg (to avoid under collection) or >220 μM/kg (to avoid over collection over 24 hours); known or suspected UTI; documented proteinuria at booking; delivered elsewhere	117	P/Cr spot test
Lamontagne, 2014 ¹⁰⁷ Good	Diagnostic accuracy	November 2005-November 2006	Canada	Women age ≥18 years, in their second or third trimester of pregnancy, ambulatory, and had an indication for a 24-hour urine collection as part of an investigation for PE	Serum Cr >150 μmol/L, history of renal transplant, preexisting microalbuminuria or proteinuria, macroscopic hematuria, or known UTI. Specimens discarded if UTI, hematuria, vaginal bleeding, rupture of membranes, labor, or induction of labor occurred during 24-hour collection; incomplete urine defined as Cr <10 mmol/kg of pre-pregnancy weight	91	P/Cr spot ratio
Verdonk, 2014 ¹¹¹ Good	Diagnostic accuracy	NR, but 2-year study	Netherlands	Women with suspected PE (de novo HTN with BP ≥140/90 mm Hg after 20 weeks' gestation and a urine protein dipstick reading ≥1+) admitted as inpatients; pregnant women with chronic HTN who developed new-onset proteinuria after mid-gestation also invited to participate	UTI, preexisting proteinuria, delivery before the 24-hour urinary collection was completed	105	P/Cr spot test

Appendix F Table 1. Study Design Characteristics of Included Studies (Key Questions 1a, 3, 4a, and 5)

Study and Quality	Study Design	Study Period	Country	Inclusion Criteria	Exclusion Criteria	n	Group
Dwyer, 2008 ¹⁰⁵ Good	Diagnostic accuracy	September 2002-March 2004	United States	All pregnant women being evaluated for PE, regardless of the alerting signs or symptoms, suspected severity or comorbid conditions	If urinalysis contained >10 white blood cells per high-power field, if a catheter was not used after membrane rupture or if an outpatient 24-hour collection was incomplete (complete collection defined as total Cr >1000 mg [850 mg for obese women] or total Cr 13 mg per kg body weight); in general, if a 24-hour urine protein not done, urinalysis not done, P/Cr ratio not done.	116	P/Cr spot test
Durnwald, 2003 ¹⁰⁴ Fair	Diagnostic accuracy	January 2001 to July 2002	United States	Women at ≥24 weeks' gestation who were undergoing evaluation for suspected PE (≥1 of the following findings: HTN, edema, new-onset proteinuria on urinary dipstick)	Concurrent diagnosis of chronic HTN, DM, or preexisting renal disease; documented preexisting proteinuria (1+ urine dipstick on initial office visit)	220	P/Cr spot ratio
Valdes, 2015 ¹¹⁹ Fair	Diagnostic accuracy	January-December 2012	Chile	Women admitted to the maternity unit of the Hospital Clinico Universidad de Chile with a diagnosis of pregnancy hypertensive disorder	Twin pregnancies, fetal birth defects (antenatal diagnosis or diagnosed during the neonatal period), chronic nephropathies, maternal age <18 years, gestational age <20 weeks, incomplete demographic and perinatal data	72	P/Cr spot test
<i>Albumin:creatinine spot urine tests</i>							
Wagh, 2005 ⁹⁴ Good	Diagnostic accuracy	October 2000-June 2001	United Kingdom	Pregnant women >20 weeks' gestation referred for assessment of de novo HTN occurring for the first time to the day assessment unit if they had an estimated and sustained SBP >140 mm Hg or a DBP of >90 mm Hg using mercury sphygmomanometry	Preexisting HTN	171	Dipstick-Microalbustix (visual) Dipstick-Clinitek Microalbumin (automated) DCA 2000-POC test
Kyle, 2008 ¹⁰⁶ Fair	Diagnostic accuracy	NR	New Zealand	Pregnant women attending a high-risk obstetric medical antenatal clinic if they had automated dipstick analysis of ≥1+ of new-onset proteinuria on a midstream urine specimen; group of negative or	Positive urine culture for UTI, underlying proteinuric renal disease, those with diabetes with an abnormal albumin/Cr in the 1st trimester.	150	Albumin/Cr spot test

Appendix F Table 1. Study Design Characteristics of Included Studies (Key Questions 1a, 3, 4a, and 5)

Study and Quality	Study Design	Study Period	Country	Inclusion Criteria	Exclusion Criteria	n	Group
				trace proteinuria women on automated dipstick also recruited; women attending clinic included those with pre-existing HTN, preexisting DM, gestational DM, renal disease, connective tissue disorders, and other high-risk obstetric and fetal conditions.			
<i>Protein dipsticks</i>							
Waugh, 2001 ¹¹² Fair	Diagnostic accuracy	NR	United Kingdom	Pregnant women presenting either for assessment of HTN in pregnancy or as referrals to the antenatal HTN clinic, >20 weeks' gestation	NR	197	Dipstick
Kyle, 2008 ¹⁰⁶ Fair	Diagnostic accuracy	NR	New Zealand	Pregnant women attending a high-risk obstetric medical antenatal clinic if they had automated dipstick analysis of $\geq 1+$ of new-onset proteinuria on a midstream urine specimen; group of negative or trace proteinuria women on automated dipstick also recruited; women attending clinic included those with pre-existing HTN, preexisting DM, gestational DM, renal disease, connective tissue disorders, and other high-risk obstetric and fetal conditions.	Positive urine culture for UTI, underlying proteinuric renal disease, those with diabetes with an abnormal albumin/Cr in the 1st trimester.	150	Dipstick
Waugh, 2005 ⁹⁴ Good	Diagnostic accuracy	October 2000-June 2001	United Kingdom	Pregnant women >20 weeks' gestation referred for assessment of de novo HTN occurring for the first time to the day assessment unit if they had an estimated and sustained SBP >140 mm Hg or a DBP of >90 mm Hg using mercury sphygmomanometry	Pre-existing HTN	171	Dipstick - Multistix 8SG (automated) Dipstick - Multistix 8SG (visual) DCA 2000 - POC test

Appendix F Table 1. Study Design Characteristics of Included Studies (Key Questions 1a, 3, 4a, and 5)

Study and Quality	Study Design	Study Period	Country	Inclusion Criteria	Exclusion Criteria	n	Group
Dwyer, 2008 ¹⁰⁵ Good	Diagnostic accuracy	September 2002-March 2004	United States	All pregnant women being evaluated for PE, regardless of the alerting signs or symptoms, suspected severity, or comorbid conditions	If urinalysis contained >10 white blood cells per high-power field, if a catheter was not used after membrane rupture or if an outpatient 24-hour collection was incomplete (complete collection defined as total Cr >1000 mg [850 mg for obese women] or total Cr 13 mg per kg body weight); in general, if a 24-hour urine protein not done, urinalysis not done, P/Cr ratio not done.	116	P/Cr automated dipstick

Abbreviations: BP=blood pressure; CG=control group; Cr=creatinine; DBP=diastolic blood pressure; DM=diabetes mellitus; GDM=gestational diabetes mellitus; HTN=hypertension; IG=intervention group; NR=not reported; P=protein; PE=preeclampsia; PIH=pregnancy-induced hypertension; POC=point of care; RCT=randomized, controlled trial; SBP=systolic blood pressure; SGA=small for gestational age; UTI=urinary tract infection.

Appendix F Table 2. Baseline Characteristics of Included Studies (Key Questions 1a, 3, 4a, and 5)

Study and Quality	Maternal age, years (range)	Race/Ethnicity (%)	Gestational age, weeks (range)	HTN (%)	Diabetes (%)	BMI (kg/m ²)	Nulliparity (%)	Singleton pregnancy (%)	Suspected PE (%) or significant proteinuria(%)*	Inpatient (%)
Key Questions 1a and 5										
McDuffie, 1996 ⁹⁷ Fair	28.5 (18-39)	White: 81.0 Black: 4.3 Hispanic: 11.7 Asian: NR	8.6 (NR)	Chronic: NR Gestational: NR	Pre-existing: NR Gestational: NR	NR	48.5	99.1	NR	NR
Rhode, 2007 ¹¹⁵ Fair	24.7 (NR)	White: 10.2 Black: 9.2 Hispanic: 74.4 Asian: NR	20.4 (NR)	Chronic: NR Gestational: NR	Pre-existing: NR Gestational: NR	NR	NR	NR	NR	NR
Key Question 3										
Simeone, 2015 ¹⁰² Fair	33.4 (NR)	White: 74.9 Black: NR Hispanic: NR Asian: NR	NR (NR)	Chronic: NR Gestational: NR	Pre-existing: NR Gestational: NR	23.3	67.1	100	NR	NR
Key Question 4a (sorted by type of test)										
<i>Protein:creatinine spot urine tests</i>										
Tun, 2012 ¹¹⁰ Fair	29 (19-42)	White: 78.9 Black: 5.6 Hispanic: 2.2 Asian: 3.3	33.8 (24.0-39.0)	Chronic: 22.2 Gestational: 24.4	Pre-existing: 5.6 Gestational: 15.6	34.1	45.6	87.8	31.4	100
Stout, 2013 ¹⁰⁹ Fair	27.1 (26.0-28.6)	White: NR Black: 65.2 Hispanic: NR Asian: NR	31.8 (30.7-32.8)	Chronic: 23.9 Gestational: 2	Pre-existing: 17.7 Gestational: NR	35.5	NR	90.4	40.4	93.7
Wheeler, 2007 ¹¹³ Fair	26.6 (NR)	White: 72 Black: 27 Hispanic: 1 Asian: NR	34 (NR)	Chronic: NR Gestational: NR	Pre-existing: NR Gestational: NR	NR	56	NR	54.0	100
Young, 1996 ¹¹⁴ Fair	NR (NR)	White: NR Black: NR Hispanic: NR Asian: NR	33.4 (NR)	Chronic: NR Gestational: 57.8	Pre-existing: NR Gestational: NR	NR	NR	NR	NR	100
Kyle, 2008 ¹⁰⁶ Fair	NR (NR)	White: 90.7 Black: NR Hispanic: NR Asian: NR	34.0 (20.1-39.7)	Chronic: 12.7 Gestational: NR	Pre-existing: 4.7 Gestational: 9.3	32.5	36.7	92.0	8.7	0

Appendix F Table 2. Baseline Characteristics of Included Studies (Key Questions 1a, 3, 4a, and 5)

Study and Quality	Maternal age, years (range)	Race/Ethnicity (%)	Gestational age, weeks (range)	HTN (%)	Diabetes (%)	BMI (kg/m ²)	Nulliparity (%)	Singleton pregnancy (%)	Suspected PE (%) or significant proteinuria(%)*	Inpatient (%)
Sethuram, 2011 ¹⁰⁸ Fair	28 (17-43)	White: NR Black: NR Hispanic: NR Asian: NR	36 (24-41)	Chronic: NR Gestational: NR	Pre-existing: NR Gestational: NR	NR	62	NR	93.8	NR
Bhide, 2015 ¹⁰³ Fair	30.8 (NR)	White: NR Black: NR Hispanic: NR Asian: NR	36.1 (21.0-41.0)	Chronic: NR Gestational: NR	Pre-existing: NR Gestational: NR	28.1	NR	NR	65.0	NR
Lamontagne, 2014 ¹⁰⁷ Good	31.8 (≥ 18)	White: 62.6 Black: 28.6 Hispanic: NR Asian: NR	32.3 (NR)	Chronic: 37.4 Gestational: NR	Pre-existing: 8.8 Gestational: 16.5	29.0	46.2	95.6	47.3	62.6
Verdonk, 2014 ¹¹¹ Good	31 (IQR 28-34)	White: NR Black: NR Hispanic: NR Asian: NR	31 (IQR 29-35)	Chronic: NR Gestational: NR	Pre-existing: NR Gestational: NR	NR	56.2	NR	69.5	100
Dwyer, 2008 ¹⁰⁵ Good	30.8 (NR)	White: 40.5 Black: 12 Hispanic: 31 Asian: 16	NR (NR)	Chronic: 22.4 Gestational: NR	Pre-existing: 6.9 Gestational: NR	NR	NR	NR	48.3	100
Durnwald, 2003 ¹⁰⁴ Fair	26.1 (NR)	White: NR Black: 43.2 Hispanic: NR Asian: NR	36.5 (NR)	Chronic: 0 Gestational: NR	Pre-existing: 0 Gestational: NR	NR	NR	NR	76.4	94
Valdes, 2015 ¹¹⁹ Fair	30.5 (NR)	White: NR Black: NR Hispanic: NR Asian: NR	NR (NR)	Chronic: 100 Gestational: NR	Pre-existing: NR Gestational: NR	32.2	44.4	100	58.3	100
<i>Albumin:creatinine spot urine tests</i>										
Waugh, 2005 ⁹⁴ Good	29 (19-40)	White: 97.7 Black: NR Hispanic: NR Asian: 2.3	NR (NR)	Chronic: NR Gestational: 100	Pre-existing: NR Gestational: NR	NR	58	NR	45.0	NR
Kyle, 2008 ¹⁰⁶ Fair	NR (NR)	White: 90.7 Black: NR Hispanic: NR Asian: NR	34.0 (20.1-39.7)	Chronic: 12.7 Gestational: NR	Pre-existing: 4.7 Gestational: 9.3	32.5	36.7	92.0	8.7	0

Appendix F Table 2. Baseline Characteristics of Included Studies (Key Questions 1a, 3, 4a, and 5)

Study and Quality	Maternal age, years (range)	Race/Ethnicity (%)	Gestational age, weeks (range)	HTN (%)	Diabetes (%)	BMI (kg/m ²)	Nulliparity (%)	Singleton pregnancy (%)	Suspected PE (%) or significant proteinuria(%)*	Inpatient (%)
<i>Protein dipsticks</i>										
Waugh, 2001 ¹¹² Fair	27 (18.4-36)	White: 86.8 Black: NR Hispanic: NR Asian: NR	36.14 (24.1-39.6)	Chronic: NR Gestational: NR	Pre-existing: NR Gestational: NR	NR	37.5	NR	70.1	NR
Kyle, 2008 ¹⁰⁶ Fair	NR (NR)	White: 90.7 Black: NR Hispanic: NR Asian: NR	34.0 (20.1-39.7)	Chronic: 12.7 Gestational: NR	Pre-existing: 4.7 Gestational: 9.3	32.5	36.7	92.0	8.7	0
Waugh, 2005 ³⁴ Good	29 (19-40)	White: 97.7 Black: NR Hispanic: NR Asian: 2.3	NR (NR)	Chronic: NR Gestational: 100	Pre-existing: NR Gestational: NR	NR	58	NR	45.0	NR
Dwyer, 2008 ¹⁰⁵ Good	30.8 (NR)	White: 40.5 Black: 12 Hispanic: 31 Asian: 16	NR (NR)	Chronic: 22.4 Gestational: NR	Pre-existing: 6.9 Gestational: NR	NR	NR	NR	48.3	100

*For Key Question 4a only, all pregnant women had suspected preeclampsia; the data in this column reflects those with significant proteinuria according to the 24-hour urine collection (reference standard).

Abbreviations: BMI=body mass index; HTN=hypertension; NR=not reported; PE=preeclampsia.

Appendix F Table 3. Intervention Characteristics of Included Trials (Key Questions 1a, 3, and 5)

Study and Quality	Group	n	Group Name	Description	Provider
Key Questions 1a and 5					
McDuffie, 1996 ⁹⁷ Fair	IG	1165	9 perinatal visits	Experimental schedule consisted of visits at 8, 12, 16, 24, 28, 32, 36, 38 and 40 weeks (total of nine visits) with ongoing risk assessment. For parous women, a telephone call was scheduled at 12 weeks instead of a visit. Since not all women presented at 8 weeks of gestation: 7-8 weeks seen according to schedule; 9-10 weeks asked to return at 14 weeks and have blood drawn at 16 weeks; 11-12 weeks asked to return at 16 weeks. Visits ranged from 45 minutes (intake) to 10-15 minutes with practitioners or physicians.	OBGYN, NPs, PA, or nurse midwives
	CG	1163	Usual care	Routine clinical schedule consisted of visits every 4 weeks from 8 to 28 weeks, then every 2 weeks until 36 weeks and weekly thereafter (total of 14 visits) with ongoing risk assessment. Since not all women presented at 8 weeks of gestation: 7-8 weeks seen according to schedule; 9-10 weeks asked to return at 14 weeks and have blood drawn at 16 weeks; 11-12 weeks asked to return at 16 weeks. Visits ranged from 45 minutes (intake) to 10-15 minutes with practitioners or physicians.	OBGYN, NPs, PA, or nurse midwives
Rhode, 2007 ¹¹⁵ Fair	IG	1251	Indicated urine testing	Women who were enrolled and delivered on or after August 15, 2002. Indicated urine testing was substituted for routine urine screening; a urine specimen was obtained prior to the patient's visits with a care provider whenever any of the criteria were present (first prenatal visit, patient complaint of symptoms of UTI, patient complaint of severe vomiting, weight loss \geq 0.9 kg since previous visit, SBP \geq 140 mm Hg, DBP \geq 90 mm Hg, or any pregnancy requiring periodic urine testing such as chronic HTN and renal disease). Chemical reagent strips use for all urine tests, mean (SD) number of test strips: 1.4 (1.3), range, 0-16. Indications for urine test also reported.	NR
	CG	1160	Routine urine screening	Women who were enrolled and delivered prior to August 15, 2002. First prenatal visit included routine urine screening, a urine culture and blood pressure determination; urine screening and BP determination were included in all subsequent visits. Chemical reagent strips use for all urine tests, mean (SD) number of test strips: 7.8 (3.4), range, 0-19.	NR
Key Question 3					
Simeone, 2015 ¹⁰² Fair	IG	140	High-risk women	At screening, women were informed about PE and its consequences by trained midwives; counseling concerned the concept of risk, the parental expectations of the screening, and the consequences of a positive test. High-risk women underwent a followup protocol consisting of daily aspirin (150 mg) from the day of screening until 36 weeks gestation and second trimester ultrasound at 20-22 weeks including UtA Doppler velocimetry. Dietary calcium intake was evaluated in each case and when $<$ 3 daily products/day, a supplementation w/ 1 g/day was recommended. Pts w/ normal second trimester UtA mean pulsatility index ($<$ 95th percentile) underwent a subsequent ultrasound and blood/urine test at 28 and 32 weeks, whereas those w/ abnormal results underwent same evaluation at 24, 28, 32 and 36 weeks.	Trained midwives
	CG	140	Low-risk women	At screening, women were informed about PE and its consequences by trained midwives; counseling concerned the concept of risk, the parental expectations of the screening, and the consequences of a positive test.	Trained midwives

Abbreviations: BP=blood pressure; CG=control group; DBP=diastolic blood pressure; HTN=hypertension; IG=intervention group; NP=nurse practitioner; NR=not reported; OBGYN=obstetrician/gynecologist; PA=physician's assistant; PE=preeclampsia; pts=participants; SD=standard deviation; SBP=systolic blood pressure; UtA=uterine artery; UTI=urinary tract infection.

Appendix F Table 4. Results of Diagnostic Accuracy Studies (Key Question 4a): Significant Proteinuria

Study and Quality	Threshold*	n	tp	fp	fn	tn	Sensitivity†	Specificity†	PPV†	NPV†
P:Cr Spot Urine Tests										
Tun, 2012 ¹¹⁰ Fair	17.0 mg/mmol	86	24	30	3	29	89	49	32	91
Stout, 2013 ¹⁰⁹ Fair	>9.0 mg/mmol	356	140	180	4	32	97	15	44	86
	>13.6 mg/mmol	356	130	129	14	83	90	39	50	86
	>21.5 mg/mmol	356	112	64	32	148	78	70	64	82
	>45.2 mg/mmol	356	72	17	72	195	50	92	81	74
	>50.9 mg/mmol	356	68	8	76	204	47	96	88	73
Wheeler, 2007 ¹¹³ Fair	>134.5 mg/mmol	356	44	2	98	212	31	>99	96	67
Wheeler, 2007 ¹¹³ Fair	23.7 mg/mmol	126	59	13	9	45	86.8	77.6	81.9	83.3
Young, 1996 ¹¹⁴ Fair	≥5.7 mg/mmol	45	NR	NR	NR	NR	100	0	NR	NR
	≥11.3 mg/mmol	45	NR	NR	NR	NR	96	18	NR	NR
	≥17.0 mg/mmol	45	NR	NR	NR	NR	91	41	NR	NR
	≥22.6 mg/mmol	45	NR	NR	NR	NR	78	59	NR	NR
	≥28.3 mg/mmol	45	NR	NR	NR	NR	65	82	NR	NR
	≥33.9 mg/mmol	45	NR	NR	NR	NR	57	100	NR	NR
Kyle, 2008 ¹⁰⁶ Fair	≥39.6 mg/mmol	45	NR	NR	NR	NR	48	100	NR	NR
Kyle, 2008 ¹⁰⁶ Fair	≥30 mg/mmol	150	12	4	1	133	92.3	97.1	75.0	99.3
Sethuram, 2011 ¹⁰⁸ Fair	>30 mg/mmol	32	25	0	5	2	83	92	NR	NR
Bhide, 2015 ¹⁰³ Fair	≥18 mg/mmol	117	76	17	0	24	100	59.6	NR	NR
	≥30 mg/mmol	117	72	9	4	32	95	78	NR	NR
	≥60 mg/mmol	117	57	0	19	41	74.5	100	NR	NR
Lamontagne, 2014 ¹⁰⁷ Good	≥30 mg/mmol	65	28	0	3	34	90	100	100	92
	≥30 mg/mmol [§]	26	7	1	5	13	58	93	88	72
	≥30 mg/mmol	91	35	1	8	47	81	98	97	86
Verdonk, 2014 ¹¹¹ Good	≥30 mg/mmol [¶]	104	68	7	4	25	94	78	NR	NR
	≥35.4 mg/mmol	104	67	3	5	29	93	91	NR	NR
	≥30 mg/mmol ^{**}	105	65	8	8	24	89	75	NR	NR
	≥50.4 mg/mmol ^{**}	105	59	1	14	31	81	97	NR	NR
	≥30 mg/mmol ^{††}	105	70	7	3	25	96	78	NR	NR
Dwyer, 2008 ¹⁰⁵ Good	≥42.4 mg/mmol ^{††}	105	69	4	4	28	95	88	NR	NR
	≥17.0 mg/mmol	116	54	28	2	32	96	53	66	94
	≥19.2 mg/mmol	116	51	25	5	35	91	58	67	88
	≥21.5 mg/mmol	116	50	18	6	42	89	70	74	88
	≥27.1 mg/mmol	116	41	8	15	52	73	87	84	78

Appendix F Table 4. Results of Diagnostic Accuracy Studies (Key Question 4a): Significant Proteinuria

Study and Quality	Threshold*	n	tp	fp	fn	tn	Sensitivity†	Specificity†	PPV†	NPV†
	≥31.6 mg/mmol	116	37	3	19	57	66	95	93	75
	≥44.1 mg/mmol	116	31	0	25	60	55	100	100	71
Durnwald, 2003 ¹⁰⁴	≥17.0 mg/mmol	220	156	35	12	17	92.9	32.7	81.7	58.6
Fair	≥22.6 mg/mmol	220	152	27	16	25	90.5	48.1	84.9	61.0
	≥33.9 mg/mmol	220	136	23	32	29	81.0	55.8	85.5	47.5
	≥44.1 mg/mmol	220	122	14	46	38	72.6	73.1	89.7	45.2
	≥45.2 mg/mmol	220	120	12	48	40	71.4	76.9	90.9	45.5
	≥ 56.5 mg/mmol	220	106	9	62	43	63.1	82.7	92.2	41.0
Valdes, 2015 ¹¹⁹	≥40.7 mg/mmol	72	31	3	11	27	73	91	95	62
Fair										
A:Cr Spot Urine Tests										
Waugh, 2005 ⁹⁴	2.0 mg/mmol	171	72	6	5	88	94	94	92	95
Good	≥3.4 mg/mmol ^{††}	171	45	16	32	78	58	83	NR	NR
	≥3.4 mg/mmol ^{§§}	171	38	16	39	78	49	83	NR	NR
Kyle, 2008 ¹⁰⁶	≥2.0 mg/mmol	150	13	44	0	93	100	67.9	22.8	100
Fair	≥3.5 mg/mmol	150	13	17	0	120	100	87.6	43.3	100
	≥8.0 mg/mmol	150	13	5	0	132	100	96.4	72.2	100
Dipstick										
Waugh, 2001 ¹¹²	≥1+ [‡]	197	31	1	76	89	29.0	98.9	96.9	53.9
Fair	≥1+ [‡]	197	30	2	13	152	69.8	98.7	93.8	92.1
	≥1+	197	31	1	107	58	22.5	98.3	96.9	35.2
	≥1+	197	28	4	21	144	57.1	97.3	87.5	87.3
Kyle, 2008 ¹⁰⁶	1+	150	13	87	0	50	100	36.5	13.0	100
Fair										
Waugh, 2005 ⁹⁴	1+ ^{¶¶}	171	63	18	14	76	82	81	NR	NR
Good	1+ ^{***}	171	39	21	38	73	51	78	NR	NR
Dwyer, 2008 ¹⁰⁵	≥1+	116	23	0	33	60	41	100	100	65
Good	≥2+	116	13	0	43	60	23	100	100	58
	≥3+	116	7	0	49	60	11	100	100	55
	≥negative	116	56	60	0	0	100	0	48	NC

*We converted all urine excretion ratios to g/mmol by converting any values to mg/g and multiplying this value by 0.113.

†Study-reported.

‡Reference standard used concentration, not excretion.

§First morning void sample.

|| Other void samples.

¶ Evening sample (5 pm).

** Morning sample (8 am).

†† Noon sample (12 pm).

‡‡ Clinitek Microalbumin (automated) dipstick (ACR).

Appendix F Table 4. Results of Diagnostic Accuracy Studies (Key Question 4a): Significant Proteinuria

§§ Microalbumin (visual) dipstick (ACR).

||| DCA 2000 - POC test.

¶¶ Multistix 8SG (automated) (ACR) dipstick.

*** Multistix 8SG (visual) (ACR) dipstick.

Abbreviations: A=albumin; Cr=creatinine; fn=false negative; fp=false positive; P=protein; tn=true negative; tp=true positive.

Appendix F Table 5. Results of Diagnostic Accuracy Studies (Key Question 4a): Severe Proteinuria

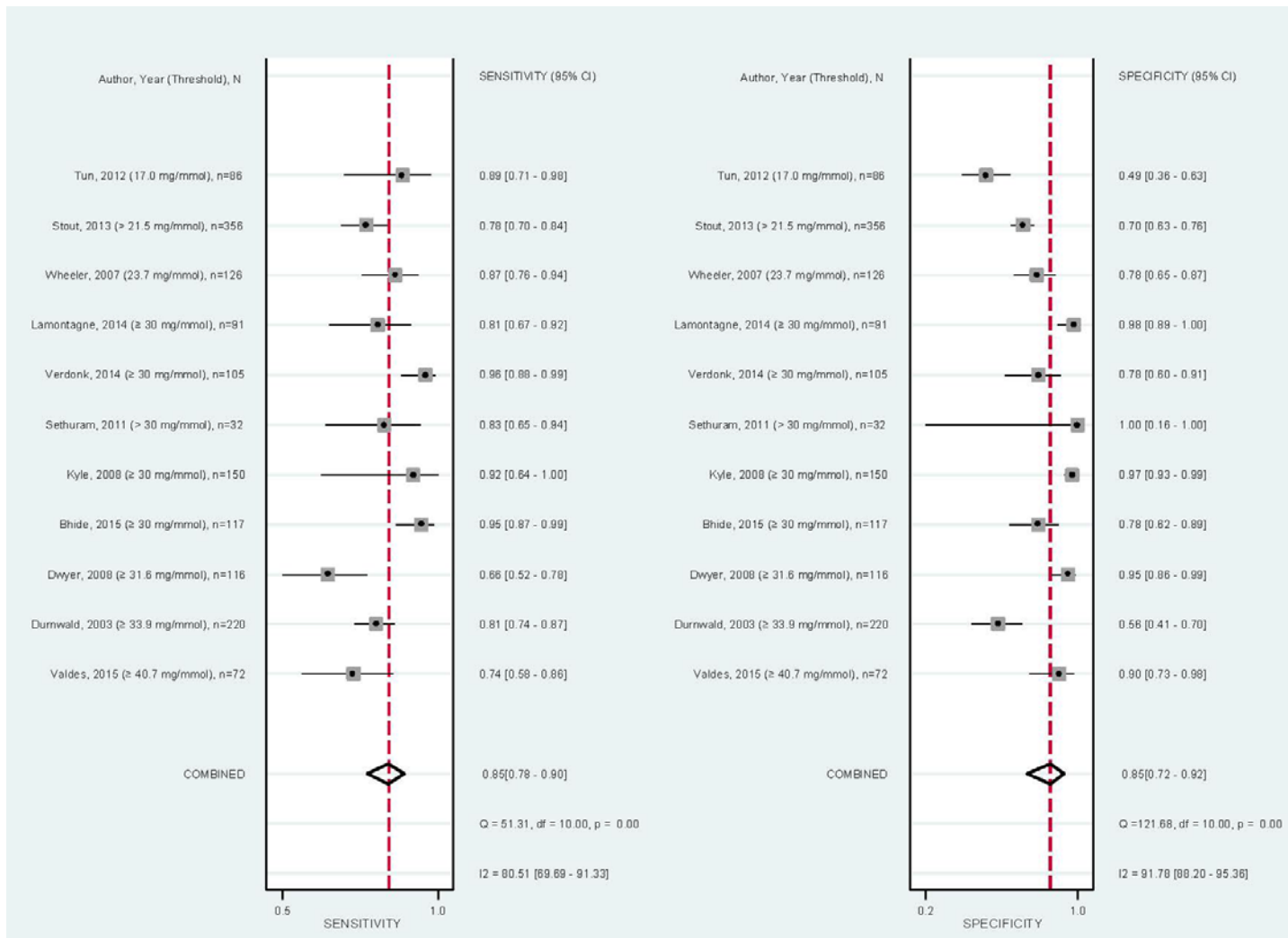
Study and Quality	Index Test	Threshold*	n	tp	fp	fn	tn	Sensitivity [†]	Specificity [†]	PPV [†]	NPV [†]
Durnwald, 2003 ¹⁰⁴ Fair	P/Cr spot	≥214.7 mg/mmol	220	15	34	3	168	83.7	83.3	31.3	98.3
		≥565.0 mg/mmol	220	13	8	5	194	72.2	96.0	61.9	97.5
Dwyer, 2008 ¹⁰⁵ Good	Dipstick	≥1+	116	3	18	0	95	100	83	14	100
		≥2+	116	3	9	0	104	100	92	25	100
		≥3+	116	3	2	0	111	100	98	60	100
		≥negative	116	3	113	0	0	100	0	3	NC
	P/Cr spot	≥226.0 mg/mmol	116	3	5	0	108	100	96	38	100
		≥339.0 mg/mmol	116	3	3	0	110	100	97	50	100
		≥452.0 mg/mmol	116	3	2	0	111	100	98	60	100
		≥565.0 mg/mmol	116	3	0	0	113	100	100	100	100
	≥1528.9 mg/mmol	116	2	0	1	113	67	100	100	99	
Valdes, 2015 ¹¹⁹ Fair	P/Cr spot test	≥517.5 mg/mmol	72	17	3	0	52	100	95	73	100
Wheeler, 2007 ¹¹³ Fair	P/Cr spot	52.0 mg/mmol	NR	NR	NR	NR	NR	87.5	82.4	53.8	96.6
		92.7 mg/mmol	NR	NR	NR	NR	NR	100	94.8	62.5	100
		339.0 mg/mmol	NR	NR	NR	NR	NR	100	100	100	100

*We converted all urine excretion ratios to g/mmol by converting any values to mg/g and multiplying this value by 0.113.

†Study-reported.

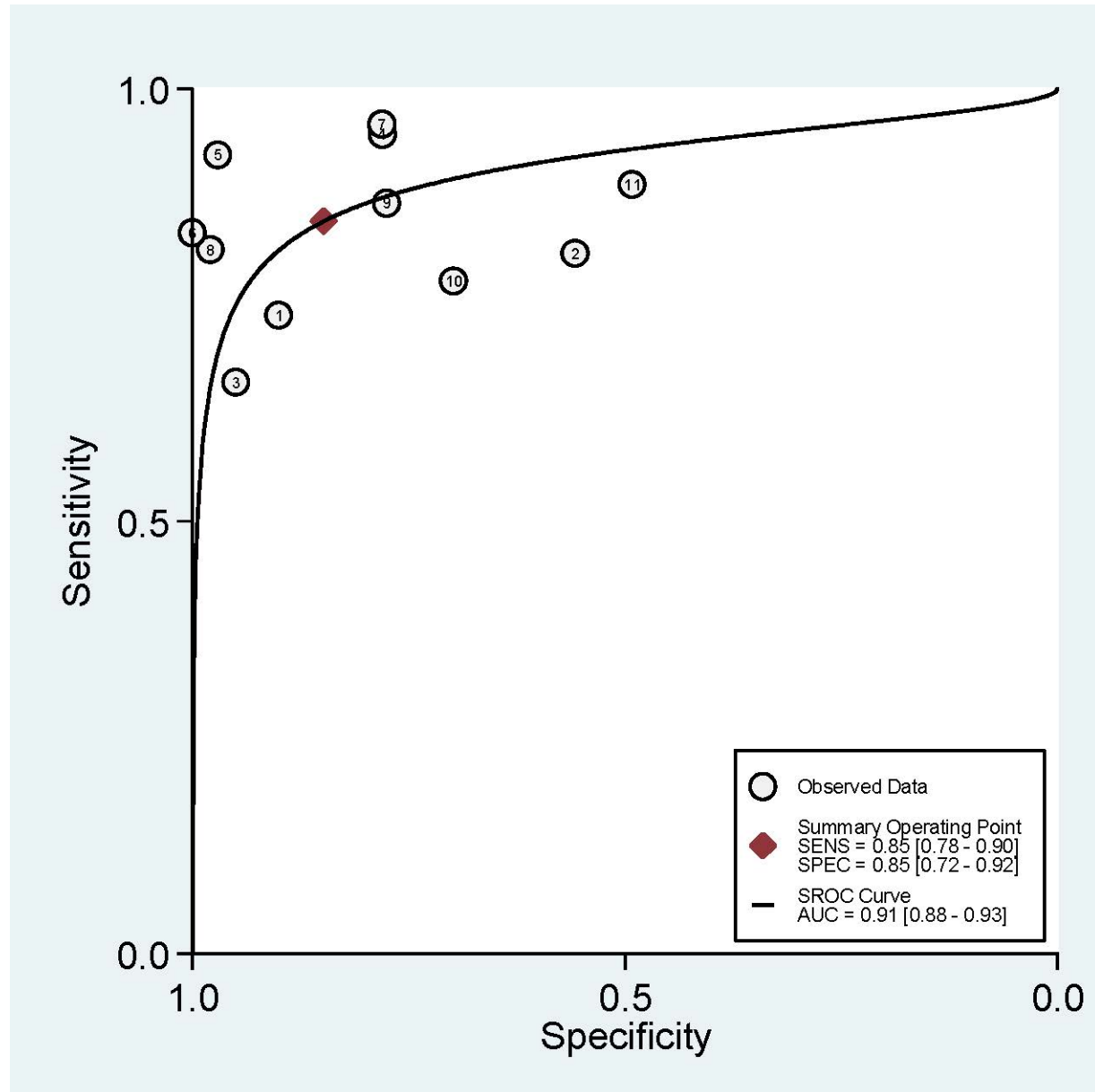
Abbreviations: A=albumin; Cr=creatinine; fn=false negative; fp=false positive; P=protein; tn=true negative; tp=true positive.

Appendix F Figure 1. Diagnostic Accuracy of Protein:Creatinine Spot Urine Tests (Key Question 4a), Sorted by Threshold



Abbreviations: CI=confidence interval; df=degrees of freedom; N=number of participants.

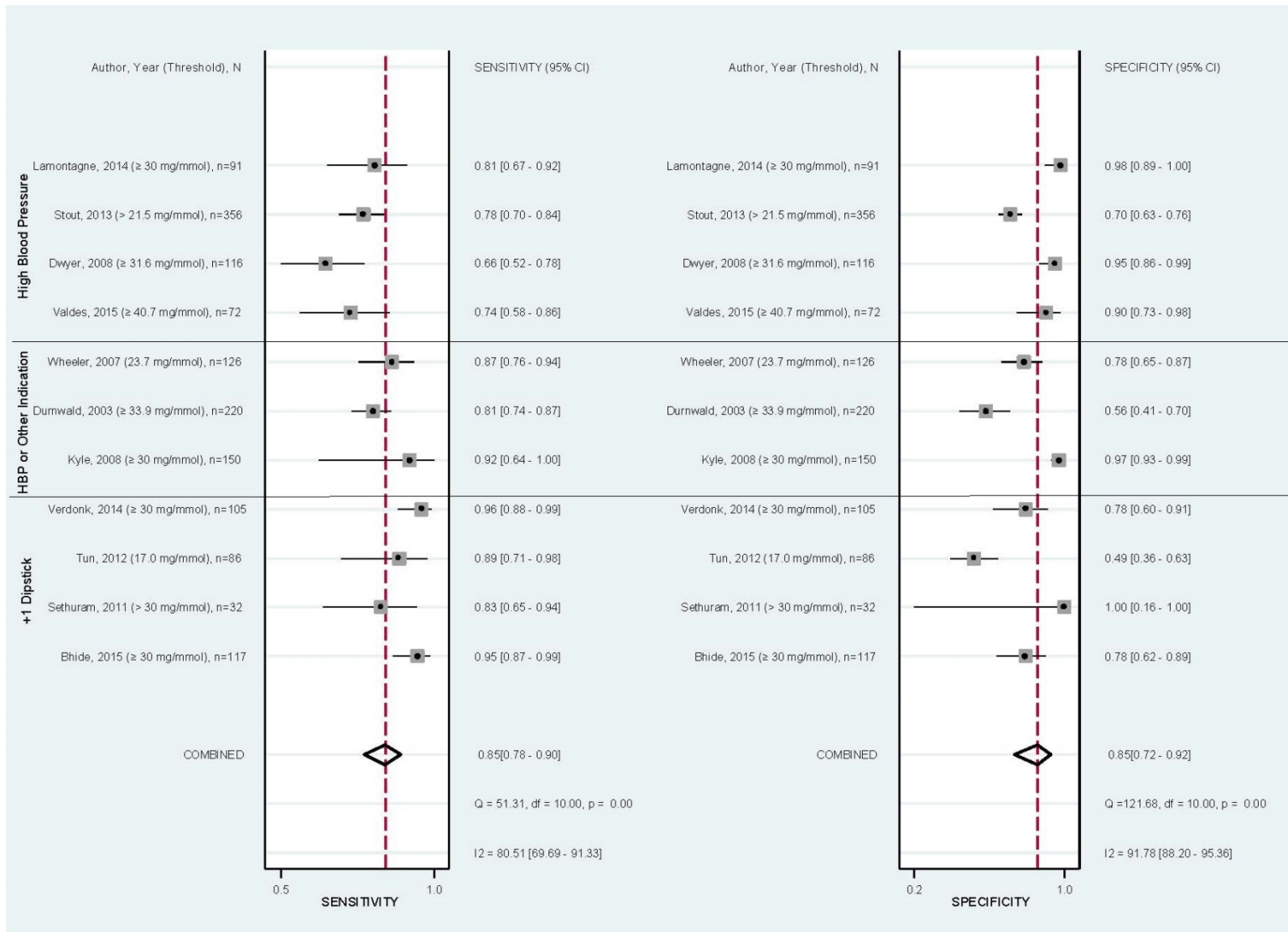
Appendix F Figure 2. Summary Receiver Operative Characteristics of Protein:Creatinine Spot Urine Tests (Key Question 4a)



Abbreviations: AUC=area under curve; sens=sensitivity; spec=specificity; SROC=summary receiver operating characteristics.

(1) Valdes, 2015; (2) Durnwald, 2003; (3) Dwyer, 2008; (4) Bhide, 2015; (5) Kyle, 2008; (6) Sethuram, 2011; (7) Verdonk, 2014; (8) Lamontagne, 2014; (9) Wheeler, 2007; (10) Stout, 2013; (11) Tun, 2012; (12) Young, 1996 (not plotted).

Appendix F Figure 3. Diagnostic Accuracy of Protein:Creatinine Spot Urine Tests (Key Question 4a), Sorted by Study Population



Abbreviations: CI=confidence interval; df=degrees of freedom; N = number of participants.

Appendix G Table 1. Test Performance Characteristics of Externally Validated Preeclampsia Risk Prediction Models

External Validation Studies Models	Oliveira 2014 ⁹⁹ Baltimore, MD PE requiring delivery: <34 weeks' gestation (early) ≥34 weeks' gestation (late)	Park 2013 ¹⁰⁰ Sydney, Australia PE requiring delivery: <34 weeks' gestation (early)	Skrastad 2014 ¹⁰¹ Trondheim, Norway PE requiring delivery: <37 weeks' gestation (early) <42 weeks' gestation (any) >34 weeks' gestation (late)	Farina 2011 ⁹⁸ Bologna, Italy PE diagnosis: >34 weeks' gestation
Caradeux 2013 ¹²¹ Santiago and Valdivia, Chile [clinical history and Doppler] [§] <i>Women presenting for 11 to 14 weeks ultrasound in pregnancy</i> N=627 % early PE=1.4 (9 cases)	N=2,962 % early PE=1.0 (30 cases) C*=NR AUC=0.69 (0.59-0.80) <i>early</i> DR=30 (CI not reported) [history, Doppler]			
Odibo 2011 ¹²² St. Louis, MO [clinical history, serum, and Doppler] [§] <i>Women presenting for 1st trimester aneuploidy screening in pregnancy</i> N=452 % early PE=2.7 (12 cases)	N=871 % early PE=1.2 (10 cases) C=NR AUC=0.86 (0.73-0.99) <i>early</i> DR=80 (CI not reported) [history, serum, Doppler]			
Parra-Cordero 2013 ¹²⁴ Santiago, Chile [clinical history, serum, and Doppler] [§] <i>Asymptomatic women undergoing routine Doppler scan at 11+0 to 13+6 weeks in pregnancy</i> N=5,367 % early PE=0.3 (17 cases)	N=1,558 % early PE=1.1 (17 cases) C=NR AUC=0.70 (0.58-0.83) <i>early</i> DR=29 (CI not reported) <i>early</i> [history, serum, Doppler]			

Appendix G Table 1. Test Performance Characteristics of Externally Validated Preeclampsia Risk Prediction Models

External Validation Studies Models	Oliveira 2014 ⁹⁹ Baltimore, MD PE requiring delivery: <34 weeks' gestation (early) ≥34 weeks' gestation (late)	Park 2013 ¹⁰⁰ Sydney, Australia PE requiring delivery: <34 weeks' gestation (early)	Skrastad 2014 ¹⁰¹ Trondheim, Norway PE requiring delivery: <37 weeks' gestation (early) <42 weeks' gestation (any) >34 weeks' gestation (late)	Farina 2011 ⁹⁸ Bologna, Italy PE diagnosis: >34 weeks' gestation
Parra-Cordero 2013 ¹²⁴ Santiago, Chile [clinical history, serum, and Doppler] [§] <i>Asymptomatic women undergoing routine Doppler scan at 11+0 to 13+6 weeks in pregnancy</i> N=5,367 % late PE=1.0 (53 cases)	N=1,558 % late PE=5.0 (78 cases) C=NR AUC=0.61 (0.55-0.68) <i>late</i> DR=18 (CI not reported) <i>late</i> [history, serum, Doppler]			
Poon 2009 ¹²⁸ [#] London, UK [clinical history and Doppler] [§] <i>Women presenting for first routine hospital visit in pregnancy</i> N=8,061 % early PE=0.5 (37 cases)	N=2,962 % early PE=1.0 (30 cases) C=NR AUC=0.78 (0.69-0.88) <i>early</i> DR=53 (CI not reported) [history, Doppler]			
Scazzocchio 2013 ^{130**} Barcelona, Spain [clinical history and Doppler] [§] <i>Women with singleton pregnancies presenting for routine 1st trimester screening</i> N=5,170 % early PE=0.5 (26 cases)	N=2,962 % early PE=1.0 (30 cases) C=NR AUC=0.77 (0.67-0.86) <i>early</i> DR=43 (CI not reported) <i>early</i> [history, Doppler]			
Scazzocchio 2013 ¹³⁰ Barcelona, Spain [clinical history and Doppler] [§] <i>Women with singleton pregnancies presenting for routine 1st trimester screening</i> N=5,170 % late PE=2.1 (110 cases)	N=2,833 % late PE=4.1 (116 cases) C=NR AUC=0.69 (0.64-0.75) <i>late</i> DR=31 (CI not reported) <i>late</i> [history, Doppler]			

Appendix G Table 1. Test Performance Characteristics of Externally Validated Preeclampsia Risk Prediction Models

External Validation Studies Models	Oliveira 2014 ⁹⁹ Baltimore, MD PE requiring delivery: <34 weeks' gestation (early) ≥34 weeks' gestation (late)	Park 2013 ¹⁰⁰ Sydney, Australia PE requiring delivery: <34 weeks' gestation (early)	Skrastad 2014 ¹⁰¹ Trondheim, Norway PE requiring delivery: <37 weeks' gestation (early) <42 weeks' gestation (any) >34 weeks' gestation (late)	Farina 2011 ⁹⁸ Bologna, Italy PE diagnosis: >34 weeks' gestation
Poon 2010 ^{127 #} London, UK [clinical history, serum, and Doppler] [§] <i>Women presenting for first routine hospital visit in pregnancy</i> N=8,061 % early PE=0.5 (37 cases)	N=2,833 % early PE=1.0 (29 cases) C=NR AUC=0.80 (0.71-0.89) <i>early</i> DR=52 (CI not reported) [history, serum, Doppler]	N=3,014 % early PE=0.4 (12 cases) C=NR AUC=0.93 (0.92-0.94) <i>early</i> DR=91.7 (61.5-98.6) <i>early</i> [history, serum, Doppler]		
Akolekar 2013 ¹²⁰ London and Gillingham, UK [clinical history, serum, and Doppler] [§] <i>Women with singleton pregnancies presenting for 1st trimester aneuploidy screening</i> N=58,884 % preterm PE (<37 wks)=1.0 (568 cases)			N=541 % preterm PE (<37 wks)=0.9 (5 cases) C=NR AUC 0.94 (0.86-1.00) <i><37 wks</i> DR=80.0 (28.4-99.5) <i><37 wks</i> [history, serum, Doppler]	
Akolekar 2013 ¹²⁰ London and Gillingham, UK [clinical history, serum, and Doppler] [§] <i>Women with singleton pregnancies presenting for 1st trimester aneuploidy screening</i> N=58,884 % any PE=2.4 (1,426 cases)			N=541 % any PE=3.9 (21 cases) C=NR AUC=0.77 (0.67-0.87) <i>any</i> DR=40.0 (19.1-63.9) <i>any</i> [history, serum, Doppler]	

Appendix G Table 1. Test Performance Characteristics of Externally Validated Preeclampsia Risk Prediction Models

External Validation Studies Models	Oliveira 2014 ⁹⁹ Baltimore, MD PE requiring delivery: <34 weeks' gestation (early) ≥34 weeks' gestation (late)	Park 2013 ¹⁰⁰ Sydney, Australia PE requiring delivery: <34 weeks' gestation (early)	Skrastad 2014 ¹⁰¹ Trondheim, Norway PE requiring delivery: <37 weeks' gestation (early) <42 weeks' gestation (any) >34 weeks' gestation (late)	Farina 2011 ⁹⁸ Bologna, Italy PE diagnosis: >34 weeks' gestation
PREDICTOR algorithm [clinical history, serum, and Doppler] [§] <i>Proprietary model, derived from multiple studies, not reported in detail</i>			N=541 % any PE=3.9 (21 cases) C=NR AUC=0.74 (0.63-0.84) any DR=30.0 (11.9-54.3) any [history, serum, Doppler]	
Onwudiwe 2008 ¹²³ London, UK [clinical history and Doppler] [§] <i>Women with singleton pregnancies presenting for routine antenatal care</i> N=3,347 % late PE=2.3 (78 cases)				N=554 % late PE=7.0 (39 cases) C=NR AUC=0.85 (0.78-0.93) late DR=74.4 (60.7-88.1) [history, Doppler]
Plasencia 2008 ¹²⁵ London, United Kingdom [clinical history and Doppler] [§] <i>Women with singleton pregnancies presenting for routine antenatal care</i> N=3,107 % late PE=2.3 (71 cases)				N=554 % late PE=7.0 (39 cases) C=NR AUC=0.76 (0.67-0.84) late DR=41.0 (25.6-56.4) [history, Doppler]
Plasencia 2007 ¹²⁶ London, UK [clinical history only] [§] <i>Women with singleton pregnancies presenting for routine assessment of risk for chromosomal abnormalities</i> N=6,015 % any PE=1.8 (107 cases) % late PE=NR				N=554 % late PE=7.0 (39 cases) C=NR AUC [†] =0.72 (0.62-0.82) late DR [‡] =53.8 (38.1-69.4) [history]

Appendix G Table 1. Test Performance Characteristics of Externally Validated Preeclampsia Risk Prediction Models

External Validation Studies Models	Oliveira 2014 ⁹⁹ Baltimore, MD PE requiring delivery: <34 weeks' gestation (early) ≥34 weeks' gestation (late)	Park 2013 ¹⁰⁰ Sydney, Australia PE requiring delivery: <34 weeks' gestation (early)	Skrastad 2014 ¹⁰¹ Trondheim, Norway PE requiring delivery: <37 weeks' gestation (early) <42 weeks' gestation (any) >34 weeks' gestation (late)	Farina 2011 ⁹⁸ Bologna, Italy PE diagnosis: >34 weeks' gestation
Poon 2010 ^{127 #} London, UK [clinical history and Doppler] [§] <i>Women presenting for first routine hospital visit in pregnancy</i> N=8,061 % late PE=1.6 (128 cases)				N=554 % late PE=7.0 (39 cases) C=NR AUC=0.93 (0.88-0.98) <i>late</i> DR=84.6 (73.3-95.9) [history, Doppler]
Poon 2009 ¹¹²⁹ London, UK [clinical history and serum] [§] <i>Women with singleton pregnancies presenting for routine assessment of risk for chromosomal abnormalities</i> N=8,051 % late PE=1.5 (124 cases)				N=554 % late PE=7.0 (39 cases) C=NR AUC=0.70 (0.60-0.79) <i>late</i> DR=35.9 (20.8-51.0) [history, serum]

* A model performance measure that refers to how well predicted risks compare to observed outcomes preferably evaluated graphically by calibration plots and supplemented by a formal statistical test, the Hosmer-Lemeshow test for logistic regression and its equivalent for Cox regression.⁸³

† A test performance statistic (equivalent to the c-statistic) used to assess discrimination, a model performance measure that refers to how well a model differentiates between those with and without the outcome.⁸³

‡ The percent of cases correctly classified based on a predefined false-positive probability threshold.⁸³ Detection rates for preeclampsia in this table are based on a fixed 10% false-positive rate, which was the most commonly reported.

§ Clinical history includes maternal characteristics, medical history, and routine clinical measures (e.g., family history of PE, personal history of PE, parity, race/ethnicity, prior preterm labor, CHTN, diabetes, thrombophilia, renal disease, mode of conception, smoking status, DBP, SBP, weight, MAP, BMI). Serum markers include PAPP-A, PIGF, PP13. Doppler ultrasound includes UtA-PI. Some variables are expressed as adjusted multiples of the median.

|| Derived from the Fetal Medicine Foundation Algorithm.

¶ Leona Poon and Kyros Nicolaides are authors on many of the model development papers for preeclampsia risk assessment. They also hold patents related to the use of biological makers for prenatal screening. The Fetal Medicine Foundation (founded by Nicolaides) and PerkinElmer are assignees on several patents on prenatal screening held by Poon and Nicolaides.

Clinical history algorithm described in Poon 2010⁶⁵ and Poon 2009.¹²⁸

** This model was used in the study included for KQ3 to evaluate potential harms of risk assessment.

Abbreviations: AUC=area under the curve; BMI=body mass index; CHTN=chronic hypertension; CI=confidence interval; DBP=diastolic blood pressure; DR=detection rate; MAP=mean arterial pressure; NR=not reported; PE=preeclampsia; PIGF=placental growth factor; SBP=systolic blood pressure.