Proteinuria in pregnancy-Review

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Abstract

Proteinuria is a cardinal sign of kidney damage and a risk factor for kidney disease progression. Urinary protein excretion increases during normal pregnancy. In the recent recommendations proteinuria is no longer a mandatory diagnostic feature of preeclampsia. Since most published data are based on proteinuria being a requirement for the diagnosis of preeclampsia, removal of proteinuria renders a substantial body of evidence in need of revision. We conducted a thorough search of the literature using appropriate Mesh terms. Most published data points towards a favorable outcome of proteinuria during pregnancy. However, apart from some reports of retrospective studies, no strong evidence exists that this applies to the long-term kidney outcome. Since blood pressure is known to dip in the first trimester of pregnancy, blood pressure elevation from its nadir to the current cut off of 140/90 mmHg may be regarded as "unrecognized prodrome". More research work is needed to find more sensitive tools for screening at-risk population in genomic, proteomic, clinical and epidemiological domains.

Introduction

Proteinuria is a sign of kidney damage and identifies those at risk for worsening kidney disease. Urinary protein excretion increases in normal pregnancy from less than 150 mg/day in non-pregnant individuals to up to 300 mg/day in pregnancy. Thus, the threshold of abnormal protein excretion for the diagnosis of preeclampsia is more than 300 mg/24 hours or more than 2+ by dipstick testing according to the American College of Obstetrics and Gynecology Guidelines [1,2]. In previous versions of the guidelines, proteinuria was required for the diagnosis of preeclampsia. Under the current guidelines, preeclampsia may be diagnosed in the absence of proteinuria if hypertension plus another severe feature is present. This change was driven by two important observations. First, the severity of proteinuria is not strongly associated with adverse maternal and neonatal outcomes. Second, preeclampsia sometimes can occur in the absence of proteinuria: up to 10% of women with preeclampsia and 20% of women with eclampsia have no proteinuria on initial presentation [3,4].

Definition of proteinuria in pregnancy

American College of Obstetrics and Gynecology (ACOG) Hypertension in Pregnancy Task Force defines proteinuria in pregnancy as the new appearance of protein in the urine in amounts equal to or greater than 300 mg of protein in 24-hour collection, protein/creatinine ratio equal to or greater than 0.3 mg/mg, or +2 or more on urine dipstick testing [1,2]

Proteinuria for the diagnosis of preeclampsia

Traditionally, the diagnosis of preeclampsia in a woman without preexisting hypertension or proteinuria required the new onset of hypertension and proteinuria after 20 weeks' gestation. In 2013, the American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy presented new diagnostic criteria for preeclampsia [1], whereby preeclampsia can be diagnosed in the absence of proteinuria if other preeclampsia features are present (Table 1).

Gestational hyperfiltration

During normal pregnancy, renal plasma flow increases leading to an increase in glomerular filtration rate (GFR) of more than 50% [5]. This in turn leads to a relative decrease in concentrations of serum creatinine and urea together with an increase in protein excretion [5]. Despite the fact that most published data points towards the favorable outcome of proteinuria during pregnancy, no evidence exists that this applies to the long-term kidney outcome. The removal of proteinuria as a requirement for the diagnosis of preeclampsia in the current guidelines is mainly to increase the sensitivity of preeclampsia screening using only blood pressure. Hypertension is a late consequence of an ongoing process(es) that eventually lead(s) to blood pressure elevation. The data is lacking about the clinical manifestations of the early changes which precede overt hypertension. Since blood pressure is known to dip during the first trimester of pregnancy, blood pressure elevation from its nadir to the current cut off of 140/90 mmHg may be regarded as "unrecognized prodrome". More research work is needed to find more sensitive tools for screening at-risk population in genomic, proteomic, clinical and epidemiological domains.

Measurement of proteinuria

Several assays are currently in use for the detection of proteinuria. These assays vary in their accuracy, cost, and simplicity to perform.

Acetic acid/ Sulfosalicylic acid

In many parts of the developing world, the urine protein heat coagulation test (acetic acid test or Sulfosalicylic acid test) are routinely used to screen for proteinuria in pregnancy [6]. The method is simple and involves applying a few drops of diluted acetic acid to a 5 ml of urine in a test tube then heat the urine to below boiling point. Depending on the resultant turbidity, the presence of protein in the urine is quantified

from 1+ to 4+. This test has the advantage of being less expensive and able to detect other proteins e.g. Bence Johns protein and paraproteins while dipstick detects the only albumen. The sulfosalicylic acid test requires centrifugation of the urine followed by addition of 2.5 ml of the supernatant to 7.5 ml of 3% sulfosalicylic acid. The degree of turbidity is quantified as in table 2 [7].

Urinary dipstick

The urinary dipstick is a commonly used point-of-care semi-quantitative test for proteinuria. As we reported in our previous work, the accuracy of dipstick urinalysis in the prediction of significant proteinuria in pregnancy is poor at the 1+ threshold, with poor positive and negative predictive values for significant proteinuria [8]. We concluded that the accuracy of the dipstick test may improve at higher thresholds (greater than 1+ proteinuria) [8]. The current 2019 guidelines raised the threshold of significant proteinuria to 2+ [2].

The 24-Hour urine collection

The gold standard for quantification of proteinuria is the 24-hour urine protein collection. In additional to quantifying total protein excretion, this method also allows calculation of the creatinine clearance as an estimate of GFR. However, the 24-hour urine collection is cumbersome for the patient and is frequently inaccurate due to over collection or under collection [9]. Thus, when interpreting the results of a 24-hour urine collection, it is important to assess the completeness of the collection: the 24-hour urine creatinine excretion should be 15-20 mg creatinine/kg body weight, using pre-pregnancy weight.

Urine protein to creatinine ratio (UPCR)

The spot urine protein to creatinine ratio is a relatively reliable, accurate, and easy method to quantify proteinuria which has largely replaced the 24-hour urine collection in the non-obstetric population. Available data suggests the urine protein/creatinine ratio is accurate for proteinuria quantification in pregnancy. This assay has become the preferred method for quantifying proteinuria due to its accuracy, reproducibility and avoiding the need for the timed 24-hours urine collection.

The accuracy of UPCR in pregnancy has been extensively evaluated [10]. Most of the studies evaluating the utility of UPCR in pregnancy were performed in women with suspected preeclampsia. These studies showed that UPCR correlates well with the timed 24-hour urinary protein excretion [11]. UPCR was found valid for baseline as well as follow up proteinuria [12]. Obtaining the sample for UPCR is simple as it requires only a midstream clean-catch sample with no need for either bladder catheterization [13] or timed sampling [14].

In addition to the many studies evaluated the accuracy of UPCR, three systematic reviews were conducted and reached the same conclusion [10,15,16]. These systemic reviews also evaluated different UPCR cutoff values. From this work, it has been concluded that a UPCR > 0.7 mg protein/mg creatinine strongly predicts significant proteinuria and a UPCR < 0.15 mg protein/mg creatinine exclude significant proteinuria. In summary, most authorities accept spot UPCR ≥ 0.26 to 0.3 mg protein/mg creatinine for the diagnosis of preeclampsia [17,18].

Albumin to creatinine ratio

An alternative to the UPCR is the urinary albumin to creatinine ratio (UACR) [19]. The UACR can be measured using an automated analyzer, available as a point-of-care test. Like the UPCR, the UACR with cut off of 20 to 60 mg albumin/g creatinine accurately predicts significant proteinuria and roughly corresponds to > 300 mg protein/day by 24-hour urine collection [20,21].

The classification of proteinuria in pregnancy

Proteinuria in pregnancy can be classified into main four classes:

1-Isolated de novo proteinuria

2-De novo proteinuria associated with preeclampsia

3-Proteinuria secondary to chronic kidney disease

4-Transient proteinuria due to UTI in pregnancy

Isolated de novo proteinuria

Isolated proteinuria is defined as the appearance of new proteinuria of more than 300 mg/g Cr at any point of time during pregnancy in the absence of hypertension, UTI, systemic disease or any apparent other causes. Gestational proteinuria is a subset of isolated proteinuria which is defined as proteinuria with onset after 20 weeks in the absence of hypertension [22]. Since gestational proteinuria often progresses to preeclampsia, it is a retrospective diagnosis that may only be made postpartum if preeclampsia does not develop.

It is not clear what causes isolated proteinuria in the absence of hypertension. Some publications attribute it to maternal factors other than those involved in the pathogenesis of preeclampsia. Holston et al reported that pregnant women with isolated proteinuria have a high body mass index and low levels of circulating angiogenic factors like placental growth factor (PlGF) [23]. Some authors consider isolated proteinuria as part of the spectrum of preeclampsia while others consider it a separate pathological entity.

Table 1. American college of obstetrics and gynecology diagnostic criteria for preeclampsia.

Blood pressure	• Systolic blood pressure SBP ≥ 140 mmHg or diastolic blood pressure DBP ≥ 90 in two occasions, at least 4 hours apart after 20 weeks gestation in a woman with previously normal BP. • If SBP ≥ 160 mmHg, or DPB ≥ 110 mmHg, hypertension can be confirmed within short interval (minutes) to avoid treatment delays.
And:	
Proteinuria	• ≥ 300 mg on a 24-hour urine collection or • UPCR ≥ 0.3 mg/mg or • Urine protein dipstick reading ≥ 2+ if quantitative testing is not available*
Or in the absence of proteinuria, new onset hypertension with one of the following:	
Thrombocytopenia	• Platelet count < 100,000/microliter
Renal insufficiency	• Serum creatinine concentration > 1.1 mg/dl or • Doubling of serum creatinine concentration in the absence of other renal diseases.
Impaired liver function	• Elevation of blood concentrations of liver enzymes to twice normal values
Pulmonary edema	
Cerebral or visual symptoms	

*The threshold has been increased to +2 in the recent 2019 guidelines [2].

Table 2. Sulfosalicylic acid test quantification

Protein (mg/dl)	Degree of Turbidity
0	Clear
1–10	Opalescent
15–30	Can read print through tube
40–100	Can read only black lines
150–400	No visible black lines
> 500	Flocculent

Isolated proteinuria frequently progresses to preeclampsia [24]. Occasionally, eclampsia can occur in patients with isolated proteinuria without hypertension [24,25].

The same conclusion about the significance of proteinuria in the absence of hypertension is reported by Yadama et al. [26] from a multicenter report. They stated that "Some pregnant women develop significant proteinuria in the absence of hypertension". However, the clinical significance of isolated gestational proteinuria (IGP) is not well understood. Kattah et al. [27] conducted a prospective study in 142 women with no history of proteinuria. They reported that isolated proteinuria developed in 13% normotensive pregnancies. They found that isolated proteinuria is associated with the development of hypertension. They concluded that there may be a different mechanism that leads to the development of isolated proteinuria compared to women with preeclampsia. Akanksha S et al. [28] also reported the same he quoted that around 50% of women with isolated proteinuria in pregnancy develop preeclampsia even in the absence of hypertension [29].

Despite the fact that most published data points towards the favorable outcome of proteinuria during pregnancy [8,30] there is little data on long-term kidney outcomes. Preeclampsia increases the risk of cardiovascular disease [31-34] and end-stage kidney disease [35,36] later in life.

De novo proteinuria associated with preeclampsia

Hypertension in pregnancy is defined as blood pressure greater than 140 mmHg systolic or greater than 90 mmHg diastolic [1]. Hypertensive disorders of pregnancy are categorized into 4 groups; preeclampsia/eclampsia, chronic hypertension in pregnancy, chronic hypertension with superimposed preeclampsia, and gestational hypertension. Of these, proteinuria is common in all except gestational hypertension (in which proteinuria is, by definition, absent).

Current ACOG criteria for the diagnosis of preeclampsia require elevated blood pressure (≥ 140/90 mm Hg on at least 2 occasions 4 hours apart, after 20 weeks of gestation) and either proteinuria (≥ 300 mg on a 24-hour urine collection, UPCR ≥ 0.3 mg/mg, or urine protein dipstick reading > 2+ if quantitative testing is not available) or, in the absence of proteinuria, high blood pressure plus another severe feature: renal impairment, low platelets, impaired liver function, pulmonary edema, or cerebral or visual symptoms [1,37] (Table 1).

High blood pressure documented prior to 20 weeks gestation is likely due to chronic hypertension. Chronic hypertension may be complicated by superimposed preeclampsia. The diagnosis of superimposed preeclampsia is often challenging, but common features include new or worsening proteinuria, worsening hypertension, or the development of severe preeclampsia features (Table 1).

Gestational hypertension is defined as the new onset of hypertension without proteinuria (or other diagnostic features of preeclampsia) after 20 weeks gestation. Gestational hypertension typically resolves within 12 weeks postpartum [38]. Like isolated gestational proteinuria, gestational hypertension may be a precursor to preeclampsia.

It is worth noting that the definition of hypertension in pregnancy (systolic BP > 140 mmHg or diastolic BP > 90 mmHg) is not evidence-based. Blood pressure normally falls by up to 10-15 mmHg early in pregnancy [39]. Thus, the threshold for the definition of hypertension in pregnancy should probably be lower than the threshold in non-pregnant individuals. Thus, defining hypertension as a BP > 140/90 mmHg does not facilitate early detection of hypertensive disorders of pregnancy.

Chronic proteinuria in pregnant women with underlying kidney disease

Proteinuria in pregnancy can be caused by conditions not related to preeclampsia, such as preexisting or de novo glomerular or tubulointerstitial kidney disease. When proteinuria is documented early in pregnancy (before 20 weeks), it is called chronic proteinuria and is usually due to underlying kidney disease. When proteinuria is first documented late (after 20 weeks), it usually due to gestational proteinuria or preeclampsia.

One study included two series of pregnant patients who underwent antenatal or post-partum percutaneous renal biopsy. These women had renal disease which presented during pregnancy, with renal biopsy performed during or immediately after pregnancy [40]. A glomerular disorder was found in 95% (19/20) of pregnant women who were biopsied during pregnancy. In the women biopsied post-partum, 82.6% (62/75) had significant proteinuria (40% preeclampsia) during pregnancy not resolving post-partum. A glomerular abnormality was found in 64%. Long term follow-up for a median of 51.5 months of 47 women revealed that 29.7% (14 women) continue to have significant proteinuria, 42.6% (20 women) had a GFR < 60 ml/min/1.73 m^2 and 12.7% (6 women) reached end-stage renal disease (ESKD) [40].

Diabetes mellitus type 1 or 2 (DM 1 or 2) is a common cause of proteinuria. Pregnant diabetic and hypertensive women can have chronic proteinuria. Women with DM 1 or 2 can develop kidney disease during their fertile age. DM 1 and 2 have almost the same prevalence of moderately increased albuminuria and diabetic nephropathy in pregnant women with type 1 and type 2 diabetes [41]. Albuminuria in women with DM 1 or 2 can also be due to a glomerular disease other than diabetic nephropathy. Albuminuria that persists more than 3 months is considered chronic kidney disease (CKD) [42].

Proteinuria in pregnancy can also be secondary to chronic hypertension. The management of women with preexisting chronic hypertension in pregnancy differs from the management of women with acute hypertensive syndromes of pregnancy as women with chronic hypertension will be subjected to careful prenatal monitoring [43]. Chronic hypertensive women should ideally be evaluated prior to pregnancy, with a focus on the presence of end-organ damage, evidence of secondary causes of hypertension, medications adjustment, and counseling regarding the risk of preeclampsia and adverse fetal events in pregnancy [43].

Differentiation between secondary hypertension and the high blood pressure caused by preeclampsia syndrome: Several unique physiologic changes occur during normal pregnancy [44]. The kidney increases in size and the collecting system dilates, the renin-angiotensin-aldosterone system (RAAS) is upregulated without hypertension and the kidney hyperfilterates without long term consequences [44]. There is mild hyponatremia and respiratory alkalosis [44]. The (RAAS) upregulations begin at the time of the luteal phase of the menstrual cycle and continue to rise after fertilization together with a parallel increase in estrogen and progesterone levels [45]. Renin levels may increase by up to eight times, angiotensin up to four times, and aldosterone up to ten to twenty times normal levels [45]. The nephrologist may be consulted if the pregnant patients develop acute kidney injury (AKI), glomerulonephritis GN, refractory hypertension, reduced estimated glomerular filtration rate (eGFR), proteinuria, or occasionally

microangiopathy [46]. It is crucial, but very challenging, to differentiate between high blood pressure caused by preeclampsia syndrome and other causes of secondary hypertension e.g. hypertension secondary to renal artery stenosis. The biochemical parameters that are usually used to differentiate secondary hypertension- namely the stimulated RAAS with high renin-are also high due to the pregnancy per se. Despite RAAS stimulation, most pregnant women do not develop hypertension. It is speculated to be owing to the vasodilating effect of estrogen and/or progesterone and the ovarian-secreted gestational hormone relaxin [47]. It has been reported that this hormonal mediated systemic vasodilation decreases systolic blood pressure by about 10-15 mmHg during pregnancy [48]. The hemodynamic changes caused by this global vasodilation involve the kidneys and lead to decreased renal vascular resistance resulting in an early increase in GFR by about 25% to 50%. The resultant state of hyperfiltration is speculated to cause an increase in protein excretion in normal pregnancy [8] with no long-term consequences unlike what we see in other hyperfiltration conditions like diabetes mellitus, solitary kidney and kidney in patients with high BMI [8,49].

An increasing portion of women enter into pregnancy with pre-existing hypertension and have risk factors for essential hypertension such as obesity, race, and advanced maternal age [44]. An estimated 25% of these patients may develop a superimposed preeclampsia syndrome [8,44]. In this relatively young population, essential hypertension is less likely to have lived long enough to cause end-organ damage. In such circumstances, the development of de novo proteinuria would potentially point to the onset of an overlapping preeclampsia syndrome [44].

Proteinuria may also occur in pregnant patients who have received a kidney transplant. End-stage kidney failure disrupts normal gonadal function and renders pregnancy relatively uncommon [50]. However, following successful kidney transplantation, fertility is improved within months [51]. In the event of conception following transplantation, the impact of kidney disease on pregnancy outcomes is influenced by the degree of renal dysfunction, preexisting hypertension, and the extent of proteinuria [52]. Pregnant hypertensive women who receive a kidney transplant are at at increased risk of superimposed preeclampsia. The incidence ranges between 15 to 25% compared with 5% of normal pregnancies [53].

Proteinuria complicating UTI in pregnancy

Urinary tract infection (UTI) is common during pregnancy due to the urinary stasis and dilatation of the urinary tract [54]. Urinary tract infection can cause transient proteinuria and should be excluded prior to attributing proteinuria in pregnancy to another cause, such as chronic kidney disease or preeclampsia [55]. Cote et al reported that UTI may cause a transient rise in protein excretion (above 30 mg/mmol) thus should be ruled out [10]. Some recent data suggests an association between UTI and preeclampsia [56]. However, this data should be taken with caution.

Recommendation and conclusion

Currently, the U.S Preventive Task Force recommends screening for preeclampsia in pregnant women with blood pressure measurements throughout pregnancy. Under current guidelines preeclampsia can be diagnosed in the absence of proteinuria, raising concerns about the validity of the available body of literature which was largely built on proteinuria being a mandatory finding for the diagnosis preeclampsia.

Despite the fact that most published data points towards the favorable outcome of proteinuria during pregnancy, no evidence exists that this applies to the long-term kidney outcomes whereas data accumulates that preeclampsia increases the risk of cardiovascular disease.

Hypertension may be a late consequence of an ongoing pathology that eventually leads to blood pressure elevation. The data is lacking about the clinical manifestations of the early changes which precede overt hypertension.

Blood pressure dips below the normal values in the first trimester. It is also not clear what is normal blood pressure value for pregnant women. More research work is needed to define norms for pregnant women and the development of sensitive screening tool for population at risk.

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