Proteinuria in Pregnancy: A Review of the Literature

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Abstract

Background: Proteinuria can be encountered in pregnant and non-pregnant patients, and is a worrying feature for clinicians and pregnant ladies as it is related to preeclampsia.

Aim: Literature review on proteinuria in pregnancy.

Materials and methods: Using several search engines, information was gathered from 68 references as the foundation for the review.

Results: Proteinuria is a consequence of two mechanisms, the abnormal trans-glomerular passage of proteins due to increased permeability of the glomerular capillary wall and the impaired re-absorption by the epithelial cells of the proximal tubules. It is most commonly associated with urinary tract infections in pregnancy or longstanding renal disease, but is related to pre-eclampsia after 20 weeks gestation in the presence of hypertension. Blood vessel endothelial cell damage plus an exaggerated maternal inflammatory response leads to increased vascular permeability, vasoconstriction, reduced placental blood flow and clotting abnormalities.

Studies imply that the correlation between dipstick urinalysis and 24 hour protein estimation is weak and NICE recommend that with significant proteinuria, automated dipstick readers be used to improve the rate of false positive and false negatives and a dipstick finding of proteinuria should be confirmed by 24 hours urine collection/protein creatinine ratio. In pregnant ladies with renal disease the main aim is to have delivery at term but patients with preeclampsia quite often develop progressive disease which ends up in the need for iatrogenic delivery. In situations when it is difficult to distinguish preeclampsia from pre-existing renal disease, it is pertinent to assume a working diagnosis of preeclampsia because of its potential for rapid development of serious maternal and foetal complications. Proteinuria (or hypertension) which persists longer than 3 months post-delivery should be followed up closely.

Conclusions: The gestational age at which proteinuria is first documented is important in establishing the likelihood of preeclampsia versus other renal disease. Proteinuria prior to or early in pregnancy suggests pre-existing renal disease. In late pregnancy, the presence of hypertension or aspects of severe preeclampsia also helps to distinguish preeclampsia from underlying renal disease. Renal biopsy is best left until the post-partum period unless unexplained rapidly progressive loss of renal function is occurring.

Introduction

Proteinuria is defined as the presence of urinary protein in amounts exceeding 0.3 g in a 24 hour urine collection or in concentrations more than 1g per litre (1+ on urine dipstick). When protein excretion exceeds these levels in a pregnant women it is considered abnormal and a sign of preeclampsia after 20 weeks gestation. However, before pregnancy or before 20 weeks gestation, proteinuria is considered a sign of existing underlying renal disease. Proteinuria in pregnancy is a clinical entity which is of interest to the obstetrician, nephrologist, urologist, general physician as well as the patient's general practitioner. More importantly, it is worrying for the pregnant patient and her family. In view of this, it is pertinent to understand the pathophysiology, differential diagnosis, investigation and management of proteinuria in pregnancy. In order to understand the aforementioned aspects, there is a need to review the literature relating to proteinuria in pregnancy.

Materials and Methods

The following literature search engines were used searching for proteinuria in pregnancy: Google, Google Scholar, Educus, Up to date and Pub Med. All together, information gathered from 68 references used as foundation for the literature review. Some of these papers have been case reports and others were reviews and case studies. Thirteen papers were found to have extensively reviewed proteinuria in pregnancy and these in addition to documentation of proteinuria in two books were thoroughly scrutinized in order to document / summarise the presentation, investigation and management as well as conclusions relating to proteinuria in pregnancy.

Literature Review

Pathophysiology of proteinuria
It has been suggested that proteinuria is a consequence of two mechanisms. [1] It can be due to the abnormal transglomerular passage of proteins due to increased permeability of the glomerular capillary wall and the impaired reabsorption by the epithelial cells of the proximal tubuli. In glomerular disease, more damage to the glomerular capillary wall means the glomerular barrier is more likely to be permeated by high-molecular-weight proteins, to which the barrier is normally impermeable. [1] The increased concentration of these proteins in the tubular lumen leads to the saturation of the reabsorptive mechanism by the tubular cells and damages them. This in turn promotes the urinary excretion of all proteins, including low-molecular-weight proteins, which are reabsorbed in normal physiologic conditions. [1]

Recent clinical studies [1] showed that in patients with glomerular diseases the urinary excretion of some HMW proteins [immunoglobulins G and M (IgG and IgM)] and of some low molecular weight (LMW) proteins, γ-microglobulin, γ-microglobulin, correlates with the severity of the histologic lesions, and may predict, better than the quantity of proteinuria, the natural course, the outcome, and the response to treatment. It is suggested that some patients have already, at the time of clinical presentation, a structural damage of the glomerular capillary wall (injury of podocytes) and of the tubulointerstitium, the severity and scarce reversibility of which are reliably indicated by an elevated urinary excretion of high molecular weight (HMW) and low molecular weight (LMW) proteins. [1]

The kidney in pregnancy

There are striking functional alterations of the urinary tract both anatomical and physiological during pregnancy. The gravid kidney enlarges its length by approximately 1 cm whilst the calyces, renal pelvices and ureters all dilate markedly through both humoral and obstructive causes. [2] Marked alterations in renal haemodynamics also occur as the estimated glomerular filtration rate (eGFR) and effective renal plasma flow (ERPF) increase by approximately 50%. Creatinine clearance significantly increases by 4 weeks gestation, peaks at 9–11 weeks gestation and then is sustained until the 36th week of gestation. In the last four weeks of pregnancy creatinine clearance reduces by 15–20%. [3]

In pregnancy the renal haemodynamic changes mean that greater quantities of colloids and solute pass by the glomerular barrier. There are also changes in glomerular permeability and altered tubular reabsorption of filtered proteins that may result in increased excretion of protein. It is normal in pregnancy after 20 weeks gestation for total protein excretion to reach 0.3g over 24 hours and for urinary albumin excretion to reach 0.2g over 24 hours. [4] It has been suggested that the threshold for normal total protein excretion be lowered to 0.2g over 24 hours. [5]

Differential diagnosis: preeclampsia

Proteinuria in pregnancy has been linked to urinary tract infections and chronic renal disease, but most importantly, to preeclampsia. [6]

Preeclampsia is a multisystem disease that manifests as hypertension and proteinuria in pregnancy. It is peculiar to pregnancy, of placental origin and is only cured by delivery. Preeclampsia affects nulliparous women and is less common in multiparous women unless additional risk factors are present. [7] Regarding pathophysiology, blood vessel endothelial cell damage plus an exaggerated maternal inflammatory response leads to:

1. Increase vascular permeability causing oedema and proteinuria
2. Vasoconstriction causing hypertension, eclampsia (reduced cerebral perfusion) and liver damage
3. Reduced placental blood flow causing intrauterine growth restriction

Risk factors include nulliparity, family/previous history, older maternal age, obesity, macrovascular diseases (chronic hypertension, chronic renal disease, sickle cell disease, diabetes and autoimmune diseases such as antiphospholipid syndrome) and pregnancies with a large placenta (twin and molar pregnancy). [7]

Symptoms include headache, visual disturbance, vomiting, drowsiness, epigastric pain/tenderness and oedema.

Investigations

To confirm the diagnosis of preeclampsia, if urinalysis is positive for proteinuria, infection is excluded by urine cultures and the protein is quantified by either 24 hour urine collection or protein creatinine ratio on a single sample. More than 30mg/n-mol on protein creatinine ratio or > 0.3g/24 hour on urine collection represents significant proteinuria. [8] Blood pressure and urine is checked at every antenatal appointment. Investigations in preeclampsia also include monitoring blood tests, ultrasounds, umbilical artery Doppler scans and cardiotocography. [6]

Despite the prognostic role of proteinuria, it remains a poorly assessed clinical sign in pregnancy. Although proteinuria is best measured by biochemical assay of a 24 hour urine sample, this is impractical and
Semi-quantitative dipstick urinalysis is more common as it is easy, quick and cheap. Clinically, urinalysis is performed in an unsupervised manner by many healthcare professionals including untrained doctors, nurses and students. Many clinicians think that 1+ proteinuria on dipstick corresponds to 300 mg/24 hours total protein excretion. This assumption is flawed in that 1+ corresponds to a protein concentration of 30 mg/dl. This idea has led to a dependence on the dipstick for both clinical decision making and research definitions of preeclampsia.

Several studies have investigated the relationship between dipstick urinalysis on random voided urine samples and a subsequently collected 24-hour urine sample.

1. Kuo and associates [5] found a poor correlation with 1+ dipstick proteinuria and subsequent 24-hour protein estimation. They reported a false positive rate of 18% and a false negative rate of 40%.

2. Meyer and associates [9] in a retrospective study found that in 300 samples of urine from hypertensive pregnant women, 66% of the women had false negative dipstick urinalysis (if significant proteinuria is defined as more than or equal to 300 mg/24 hours). They reported a false positive rate of 26% at the 1+ level.

3. Brown and associates [10] produced false negative results of 8–18% and a very high false positive rate of 67% with 1+ scores. To explain the persistent false positive rate of 1 in 4, they suggested that the dipstick is too sensitive at the 1+ threshold and that it is useful for the management of preeclampsia as it will minimise the false negative results (missed proteinuria) but the test will be incorrect at least half of the time.

4. Waugh and associates [11] found a high false negative rate where up to 65% of women with <1+ proteinuria on dipstick analysis had significant proteinuria.

The studies imply that the correlation between dipstick urinalysis and 24 hour protein estimation is weak. False positive results may result in over investigation and intervention but a more serious issue is when a false negative result may place a woman and her pregnancy at risk. Reasons for the poor correlation include observer error, the characteristics of the dipstick tests, the units of protein estimation, the differing nature of the urine specimens involved, as well as possible variation in the "gold standard" assay employed in the laboratory setting.

Management

Where proteinuria is present with infection, the infection is treated needless to say. The degrees of preeclampsia are described as follows:

1. Mild – proteinuria and hypertension <170/110 mmHg
2. Moderate – proteinuria and hypertension ≥170/110 mmHg
3. Severe – proteinuria and hypertension <32 weeks gestation or with maternal complications (see below)

The complications of preeclampsia can be split into maternal and fetal complications:

- Maternal
  - Eclampsia
  - Cerebrovascular accident (CVA)
  - Haemolysis, elevated liver enzymes and low platelet count (HELLP syndrome)
  - Disseminated intravascular coagulation (DIC)
  - Liver failure
  - Renal failure
  - Pulmonary oedema

- Fetal
  - Intrauterine growth restriction
  - Preterm birth
  - Placental abruption
  - Hypoxia

Patients are investigated with a blood pressure > 140/90 mmHg but are admitted if evidence of significant proteinuria regardless of hypertension or moderate/severe preeclampsia (see above). Those without significant proteinuria on 24 hours collection can be discharged. Those with 1+ proteinuria only have their proteinuria quantified and are reviewed as outpatients.

Antihypertensives are given if blood pressures in pregnancy reach 170/110 mmHg or above. Oral nifedipine is used for initial control with intravenous labetalol as a second line in severe hypertension. Methyldopa is best used as a maintenance drug. For eclampsia, magnesium sulphate is used. However, preeclampsia and eclampsia is indefinitely cured by delivery alone. For mild preeclampsia, monitoring is best as long as there is no fetal compromise. Induction of labour at term is best. For moderate or severe
preeclampsia, delivery is required after 34 weeks gestation. Before 24 weeks, monitoring at a specialist unit is advised. [13]

Discussion

Viswanathan and Upadhyay [14] as well as Montanes Bermudes and associates [15] stated that the average daily urinary protein excretion in adults is 80 mg per day urinary protein excretion is considered to be normal when the excretion rate is less than 150 mg per day. They also stated that albumin represents 15% of the daily urinary protein excretion in healthy individuals, with other plasma proteins (for example, immunoglobulins, beta-2-microglobulin and Tamm-Horsfall protein constituting the remaining 85% and that proteinuria varies in amount (from microalbuminuria to nephritic range proteinuria), and could be transient or persistent.

Some authors [16] [17] stated that the diagnosis of chronic renal disease is made when there is urinary excretion of abnormal quantities of protein for three months or longer. Other authors [18] [19] [20] [21] stated that the presence of proteinuria is an independent factor for end-stage renal disease and death within the general population, and also in patients with chronic kidney disease.

A number of authors iterated that pharmacologic reduction of proteinuria is utilised as a surrogate marker in the management of acute glomerulonephritis and chronic renal disease and this is associated with improved renal outcomes. [22] [23] [24] [25] [26] [27]

Various types of proteinuria have been described including: microalbuminuria; overt albuminuria; nephritic range proteinuria; glomerular proteinuria; tubular proteinuria; overflow proteinuria.

Microalbuminuria which is associated with increased risk of progressive kidney disease and future cardiovascular events in many populations. Microalbuminuria is defined as urine albumin of 20 to 200 mg per gram of creatinine in men; and 30 to 300 mg per gram of creatinine in women. [28]

In overt albuminuria, urine albumin is greater than 300 mg per day. [28] In overt proteinuria urine total protein is equal to or greater than 300 mg per day. [28] In a number of renal diseases, larger amounts of proteinuria are associated with worse renal survival.

In nephrotic range proteinuria, urine total protein is equal to or greater than 3.5 grams per day and serum albumin is less than 3.0 grams per deci-litre. The presence of nephritic range-range proteinuria with oedema, hypoalbuminuria, and hyperlipidemia constitutes nephritic syndrome. [28]

In glomerular proteinuria there is passage of protein from glomerular capillary blood (mainly albumin) into the urine and the urine albumin is between 1 gram and 20 grams per day. [28]

In tubular proteinuria there is passage of low molecular weight proteins (e.g., retinol-binding protein, alpha-2-microglobulin, beta-2-microglobulin) into the urine and the urine total protein is less than 2 grams per day. [28]

In overflow proteinuria there is overproduction of small proteins (for example, myoglobin, light chains) which leads to increased glomerular filtration and appearance in the urine and in overflow proteinuria the urine total protein is up to 20 grams per day. [28]

Proteinuria can be tested by means of qualitative testing, semi-quantitative testing and quantitative testing.

In qualitative testing proteinuria is routinely detected by means of multiagent urinary dipstick testing. The presence of urinary albumin is detected by means of a colorimetric reaction with the dipstick-impregnated reagent. It has been stated that dipstick testing has limited sensitivity for nonalbumin protein, and it is hence often falsely negative in the presence of predominantly tubular or overflow proteinuria. [28]

Siedner and associates [29] as well as White and associates [30] stated that the sensitivity of the urinary dipstick for albumin ranges from 83% to 98% with a specificity of 59% to 86%. They also stated that this reaction depends upon the concentration of albumin, in such a way that testing of large-volume, dilute urine would underestimate the degree of albuminuria and similarly, testing of highly concentrated urine may overestimate the degree of albuminuria. Sperati and Fine [28] false-positive results may be obtained with markedly alkaline PH (greater than 8.0) and whilst qualitative dipstick testing is rapid, easy to perform, and commonplace, the false-negative and false-positive rates limit the utility of qualitative testing of urine for proteinuria. Sperati and Fine [28] also stated that quantification of extent of proteinuria using dipstick testing is as follows:

- Negative – 0 mg per decilitre
- Trace – 15 to 30 mg per decilitre
- 1+ - 30 to 100 mg per decilitre
- 2+ - 100 to 300 mg per decilitre
- 3+ - 300 to 1000 mg per decilitre
- 4+ - greater than 1000 mg per decilitre.

Sperati and Fine [28] iterated that in previously
sulfosalicylic acid (SSA) was added to urine specimens in order to precipitate all protein, for the detection of non-albumin proteins. They stated that the resultant turbidity is graded upon a scale of 0 to 4+ and even though SSA testing is still used, semiquantitative and quantitative testing methods have largely replaced it.

It has been stated that dipsticks that have been subsequently developed are capable of reporting albumin-to-creatinine ratios in the micro-albumin range, as well as total protein-to-creatinine ratios and standardization of the protein measurement to the quantity of creatinine in the urine does help avoid errors introduced by dilute or concentrated urine samples. Comper and Osicka [31] stated that measurement of total protein allows the detection of tubular and overflow proteinuria and the reported sensitivity of these semi-quantitative dipsticks is 80% to 97% with a specificity of 33% to 80%.

Sperati and Fine stated that quantitative measurement of urinary protein is the definitive for detecting proteinuria and for this purpose twenty-four-hour urine collections have been utilised, although these collections are prone to under-collection and over-collection. [28]. They also stated that in addition 24-hour urine collections are cumbersome for, and unpopular with patients and that reporting the 24-hour urine standardized to the 24-hour urine creatinine (grams of protein / grams creatinine) helps in adjusting for variations in the duration of collection. Sperati and Fine [28] indicated that in men, an adequate collection typically has 20 to 25 grams per kilogram and in women 15 grams to 20 grams per kilogram body weight.

Ginsberg and associates [32] suggested that the expected grams of excreted creatinine can alternatively be estimated by 140 minus age multiplied by weight / 5000 [(140-age) X weight/5000], where weight is in kilograms. This result is then multiplied by 0.85 in women. Sperati and Fine [28] stated that quite commonly, a urine-protein-creatinine ratio on a spot urine sample is being used to approximate the 24-hour urine protein excretion.

Some authors [16] [32] iterated that a first morning sample of urine most closely estimates 24-hour protein excretion, even though a random sample is acceptable if a first morning void is unavailable.

Papanna and associates [33] as well as Cote and associates [34] suggested that in view of diurnal variation, it would be best to collect spot urine samples at the same time each day if it is being used to follow up patients on long term basis. Furthermore the correlation of the spot sample with 24-hour excretion is less robust with nephrotic-range proteinuria. They also stated that the spot ratio might also be less accurate in pregnant women with greater than 300 mg of proteinuria.

Sperati and Fine [28] iterated that about 1 gram of creatinine is excreted by people whose body surface areas are 1.73 m^2 and as such a protein-to-creatinine ratio of 1 gram protein per gram of creatinine in an average-sized person approximates 1 gram of proteinuria in 24 hours. In view of this it is pertinent to appreciate that a ratio of 2.5 grams protein per gram of creatinine in a muscular person who excretes 2 grams of creatinine in 24 hours may actually represent nephrotic-range proteinuria of 5 grams per day. In the same token, an older, frail woman might excrete less than 1 gram of creatinine per day, and in a situation like this, the spot ratio would tend to overestimate her proteinuria. Microalbuminuria is on the whole measured on a spot urine sample which is standardized to urine creatinine.

Roberts and associates [35] iterated that glomerular filtration rate (GFR) and renal blood flow rise markedly during pregnancy, resulting in a physiologic fall in serum creatinine concentration and urinary protein excretion increases substantially as a result of a combination of increased glomerular filtration rate (GFR) and increased permeability of the glomerular basement membrane.

Eknoyan and associates [36] iterated that the spot urine protein-to-creatinine ratio (PC ratio) has become the preferred method for the quantification of proteinuria in the non-pregnant population in view of high accuracy, reproducibility, and convenience in comparison with timed urine collection.

Robert and associates [37] as well as Neithanol and associates [38] stated that majority of studies that evaluated the urine protein-to-creatinine ratio (the PC ratio) were highly correlated with the 24-hour urine protein measurement as it is in non-pregnant adults. Chen and associates [39] stated that routine catheterization of the urinary bladder for the measurement of urine protein-to-creatinine ratio (the PC ratio) is not necessary, mid-stream clean-catch samples are accurate in pregnant women.

More than a dozen studies attempted to validate the urine PC ratio for the detection of abnormal proteinuria in women with hypertensive pregnancy; in most of these studies 24-hour urine collection was used as the "gold standard" [38] [40] [41] [42] [43] [44] [45] [46] [47] [48] [49] [50] [51] [52]. Two systematic reviews evaluated the literature and arrived at similar
conclusions as follows:

1. Côté and associates [34] iterated that the spot urine ratio had a pooled sensitivity of 83.6 percent (95% CI 77.5-89.7) and specificity of 76.3 percent (95% CI 72.6%-80.0) using a cut-off of 30 mg protein per m-mol creatinine (0.26 mg protein per mg creatinine) to predict proteinuria greater than 300 mg per day by 24-hour urine collection. They concluded that a low spot protein creatinine ratio is a reasonable “rule-out” test for excluding proteinuria greater than 300 mg/day in hypertensive pregnancy.

2. Pappanna and associates [33] observed that a lower cut-off-of 0.13 to 0.15 mg protein per mg creatinine provides higher (0 to 99 percent) sensitivity, albeit with more false-positive results (specificity 33 to 65 percent). They also observed that a higher cutoff of 0.6 to 0.7 mg protein / mg creatinine had a much higher specificity (96 percent) for significant proteinuria (greater than 300 mg in a 24-hour specimen), but at the cost of lower sensitivity (85 to 87 percent). They in addition observed that midrange protein/creatinine ratios (0.8 mg protein/mg creatinine) had poor sensitivity and specificity.

Visintin and associates stated that deductions from the above two analyses would indicate that a urine PC ratio above 0.7 mg protein per mg creatinine strongly predicts significant proteinuria while a urine PC ratio less than 0.15 mg protein per mg creatinine can be considered to be normal (predictive of less than 300 mg protein in a 24-hour collection), such that confirmatory testing with 24-hour urine collection is probably not necessary in these individuals. Women with urine PC ratio results that range between 0.15 and 0.7 mg protein/mg creatinine should have a 24-hour urine collection to accurately quantify proteinuria. In the event where a 24-hour urine collection is not obtained, the guidelines define proteinuria as random urine sample PC ratio greater than 0.26 mg protein per mg creatinine (30 mg per m-mol). [53]

Thadani and associates [54] stated that the urine albumin creatinine ratio (ACR), similar to the PC ratio, is measured by means of “spot” urine specimen. ACR which was initially developed for the detection of albuminuria in patients with diabetes mellitus, it has now been recommended as the best initial screening test for proteinuria in non-pregnant adults, in view of its increased sensitivity as compared with the PC ratio.

Kyle and associates [50] stated that ACR which can be performed by means of an automated analyzer allows immediate point-of-care testing that could be utilized in an antenatal clinic and like the PC ratio, ACR (using the threshold of ? 8.0 mg /m-mol) is strongly predictive of significant proteinuria in a high-risk obstetric antenatal clinic. Nissell and associates [55] as well as Gangeran and associates [56] also said ACR is also predictive of significant proteinuria in women with hypertensive pregnancies.

When a pregnant lady is found to have proteinuria it would pertinent to all the differential diagnoses of proteinuria in pregnancy and to determine whether or not the pregnant lady has preeclampsia. Thadani and associates stated that in patients with pre-existing established renal disease prior to conception or in whom proteinuria is documented before the 20th week of gestation, the diagnosis of pre-existing renal disease can be readily made in view of the fact that preeclampsia rarely occurs before that time. [54] They also said that on the contrary the clear documentation of new-onset proteinuria after 20 weeks of gestation, especially when it is accompanied by new-onset hypertension, would strongly suggest preeclampsia. Nevertheless, at times de novo renal diseases (for example, lupus nephritis) can occur during late pregnancy as well. In cases when information on the presence or absence of proteinuria (and hypertension) in early pregnancy is lacking, differentiating underlying renal disease from preeclampsia can be very difficult. In view of this Thadani and associates [54] advised that quantification of protein excretion in early pregnancy in women at risk for underlying renal disease (for example, women with chronic hypertension, diabetes mellitus and systemic lupus erythematosus).

Verlohren and associates [57] reported that a new serum test for early diagnosis of preeclampsia has been developed which involves the detection of abnormal levels of placentally-derived angiogenic factors, sFit1 (soluble fms-like tyrosine kinase-1) and PIGF (placental growth factor). Some authors stated that this new diagnostic test is available in Europe and it is being evaluated by the FDA for use in the United States of America. [58] [59] [60]

In pregnant ladies with renal disease the main aim is to have delivery at term but patients with preeclampsia quite often develop progressive disease which ends up in the need for iatrogenic delivery. In situations when it is difficult to distinguish preeclampsia from pre-existing renal disease, it is pertinent to assume a working diagnosis of preeclampsia because of its potential for rapid development of serious maternal and foetal complications. [54]

Chua and associates [60] iterated that some cases the
differentiation between preeclampsia and kidney disease can only be made retrospectively in view of the fact that signs of preeclampsia generally resolve within 12 weeks after delivery, on the other hand proteinuria due to underlying renal disease does not. They added that the resolution of proteinuria pursuant to preeclampsia, especially when severe, nevertheless, can sometimes take much longer. It has been stated that in one cohort of study involving 205 women with preeclampsia, fourteen percent had persistent proteinuria at 12 weeks post delivery, which eventually resolved by two years postpartum in all but 2 percent of subjects. [54] [61] However, proteinuria (or hypertension) which persists longer than 3 months post delivery should be followed-up closely and this should be evaluated further and appropriate referral to enable detection and treatment of underlying kidney disease or chronic hypertension. [54] [61]

It has been recommended that in situations when preeclampsia has developed in women with pre-existing renal disease and / or hypertension, this often occurs earlier in the pregnancy and may be particularly severe. In such situations, significant pointers to the diagnosis of superimposed preeclampsia can be provided by systematic manifestations of the disease, if present, such as thrombocytopenia, an increase in levels of liver enzymes, hemolysis, and / or evidence of fetal compromise (inclusive of intra-uterine growth restriction) [62]

Katz and associates [63] as well as Reece and associates [64] stated the association of worsening hypertension and proteinuria in a woman with renal disease may represent exacerbation of the underlying disease. They iterated that studies in women with documented primary renal disease prior to the pregnancy have revealed that the majority of women with glomerular disease exhibit increasing proteinuria during the course of their pregnancy and nephrotic syndrome in the third trimester.

Fisher and associates [65] iterated that severe preeclampsia is the most common cause of de novo nephrotic syndrome in pregnancy. Yang and associates [66] said that nephrotic syndrome in pregnancy could also be caused by pre-existing kidney disease during pregnancy (for example, associated with invasive trophoblastic tumours). Once heavy proteinuria is found the cause of the proteinuria may be obtained from the history and clinical examination. This is particularly pertinent in patients who have systemic disease like diabetes mellitus, systemic lupus erythematosus, HIV infection, or in cases of intake of a commonly offending drug even though this is much less common in pregnant women. (Non steroidal anti-inflammatory drugs, gold, penicillamine) In order to confirm the diagnosis in such cases renal biopsy is required. [54]

Strauch and Hayslett [67] stated that if de novo kidney disease is suspected as the cause nephrotic syndrome, a renal biopsy is an option to establish a definitive diagnosis if the patient’s management would be affected, nevertheless, this is rare. They also stated that numerous analyses have concluded that the presence of nephrotic syndrome due to renal disease, in the absence of significant renal insufficiency and / or significant hypertension, does not seem to affect the natural course of renal disease or fetal survival.

Thadani and associates [54] as well as Collins and associates [68] suggested that the management of nephrotic syndrome in pregnancy should be based upon expert opinion, in view of availability of very little data to support evidence-based practice. They also suggested that management should be aimed at reduction of oedema to a level that shows comfort during ambulation and the dietary intake of sodium may be limited to 1.5 grams of sodium per day (about 60 mEq) to reduce new oedema formation provided normal blood pressure is maintained. In addition they suggested that bed rest is a safe and often effective method to facilitate resolution of oedema. Other recommendations made by Thadani and associates [54] include: Generally, the use of diuretics should be discouraged because of the theoretical risk that they would impair the normal pregnancy-associated expansion of plasma volume, possibly leading to decrease in placental perfusion. Nevertheless, no clear evidence exists of adverse foetal effects with either thiazide diuretics or loop diuretics, and their use is occasionally indicated for severe, intractable oedema. In such cases, the therapy should be aimed at reduction of excessive oedema at a slow rate of no more than 1 to 2 pounds per day with a loop diuretic, while a low sodium diet is maintained. In cases where treatment on a chronic basis is needed, diuretic therapy should be given on alternative-day schedule in order to avoid a reduction of plasma volume and electrolyte disturbances. They also recommended that a written record of daily weights taken by the patient should be kept and that diuretics should not be used in preeclampsia because this condition is characterized by a reduction in circulating plasma volume.

Conclusions

Proteinuria is a consequence of two mechanisms, the abnormal transglomerular passage of proteins due to
increased permeability of the glomerular capillary wall and the impaired reabsorption by the epithelial cells of the proximal tubuli. Proteinuria can be quantified in many ways, through urine dipstick, 24 hours urine collection and protein creatinine ratio. It is most commonly associated with urine tract infection in pregnancy or longstanding renal disease. However, it is associated with preeclampsia after 20 weeks gestation in the presence of hypertension too. It is imperative that this proteinuria and hypertension be investigated as preeclampsia can have serious consequences for mother and pregnancy. Recommendations included an emphasis on improving diagnostic techniques to confirm proteinuria above the level of 0.3g/24 hour on a simple dipstick test meaning this would in turn remove the need for patients to wait 48 hours to establish a diagnosis of preeclampsia on 24 hour urine assay.

The gestational age at which proteinuria is first documented is important in establishing the likelihood of preeclampsia versus other renal disease. Proteinuria, which has been documented prior to pregnancy or in early pregnancy (before 20 weeks of pregnancy), suggests pre-existing renal disease. In late pregnancy the presence of hypertension or other symptoms/signs of severe preeclampsia (for example, thrombocytopenia, elevated liver transaminases), if present, also helps to distinguish preeclampsia from underlying renal disease.

Preeclampsia is the most common cause of proteinuria in pregnancy and must be excluded in all women with proteinuria first identified after 20 weeks of gestation. If preeclampsia is excluded then the presence of primary or secondary renal disease should be considered. If renal biopsy is indicated for diagnosis it is usually better to wait until the patient is postpartum unless unexplained rapidly progressive loss of renal function is occurring.

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