The management challenges of non-preeclampsia-related nephrotic syndrome in pregnancy

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Summary: Nephrotic syndrome in a pregnant woman may be challenging, especially when the onset is early in pregnancy or with severe manifestations. Preeclampsia is the most common cause of nephrotic syndrome in pregnancy; however, this review will focus on the management of other renal causes. The aim of this pragmatic review is to address clinical issues that clinicians looking after women with nephrotic syndrome may encounter during pregnancy and the postpartum period. First, we discuss some general issues regarding nephrotic syndrome and its impact on maternal and fetal outcomes in pregnancy, and then we review the maternal management of nephrotic syndrome in pregnancy and during the postpartum period.

Keywords: nephrotic syndrome, proteinuria, pregnancy

INTRODUCTION

Nephrotic syndrome is a problem physicians taking care of pregnant women are likely to encounter in their practice, as preeclampsia is the most common cause in pregnancy. In addition, women with nephrotic syndrome secondary to underlying renal disease may be seen by a variety of specialized caregivers, such as obstetric medicine physicians, nephrologists, endocrinologists, rheumatologists, obstetricians and maternal-fetal medicine specialists (MFM). When nephrotic syndrome occurs in a previously healthy woman, primary-care physicians and midwives may also be involved. The prevalence of nephrotic syndrome is difficult to estimate;¹ however, it may be increasing as women are now entering pregnancy with more medical comorbidities and at an older age. Nephrotic syndrome may be challenging, especially when the onset is early in pregnancy or with severe antepartum manifestations.

We present a pragmatic review on specific issues and challenges of nephrotic syndrome in pregnancy (not due to preeclampsia), including the common presentation and consequences of nephrotic manifestations in pregnancy. For more information on specific renal diseases in pregnancy,^{2,3} especially *de novo* renal disease, we strongly encourage the reader to seek complete information and advice from local experts and literature. As there are few evidence-based medicine-derived data to guide clinical practice for nephrotic syndrome in pregnancy, this review is based on older descriptive literature, reported case series, experts' opinions, and our own clinical experience and discussions.

GENERAL ISSUES FOR NEPHROTIC SYNDROME

Physiology of proteinuria and definition of nephrotic syndrome

Proteinuria increases through the trimesters during normal pregnancy, along with the physiological increase in renal plasma flow and glomerular filtration rate (GFR). Therefore, the upper limit for normal range of proteinuria increases from 150 mg/day outside pregnancy to 300 mg/day during pregnancy. This normal proteinuria consists of both tubular and glomerular proteinuria.⁴ When proteinuria increases above normal range, its origin may be glomerular (selective or non-selective proteinuria), tubular or overflow proteinuria (the latter is rarely encountered in young women).

Most of the time, nephrotic range proteinuria will consist of glomerular proteinuria. Nephrotic syndrome is classically defined outside pregnancy as nephrotic proteinuria (>3 g/day) with hypoalbuminaemia (serum albumin <30 g/L), oedema, hypercholesterolaemia and lipiduria. In normal pregnancy, albumin levels decrease progressively from a mean of 38 g/L at 12 weeks to 32 g/L at 36 weeks, and cholesterol levels increase from a mean of 4.48 mmol/L (173 mg/dL) at 12 weeks to 6.63 mmol/L (256 mg/dL) at 36 weeks.⁵

It is important to emphasize that high levels of proteinuria do not always lead to hypoalbuminaemia and nephrotic syndrome. In the diagnosis of nephrotic syndrome, one needs to assess the presence of clinical repercussions associated with hypoalbuminaemia and decreased oncotic pressure, such as peripheral oedema, ascites and pleural/pericardial effusions.

How nephrotic range proteinuria is found in pregnancy

In most circumstances, nephrotic range proteinuria will be detected in the setting of:

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- Routine antenatal urine dipstick screening in an asymptomatic woman;
- Focused work-up in specific high-risk population:
 - known renal disease or risk factors for renal disease (e.g. diabetes);
 - hypertensive: to rule out preeclampsia or for baseline work-up of pre-existing hypertension;
- New-onset oedema investigation.

Causes of proteinuria

The main cause of nephrotic range proteinuria in pregnancy is preeclampsia. Therefore, the cause of nephrotic syndrome in pregnancy (especially >20 weeks) should be considered as preeclampsia until proven otherwise.⁶ Glomerular diseases occurring in pregnancy could represent either pre-existing glomerulonephritis (GN) (known or unmasked by pregnancy) or *de novo* GN. The principal causes of proteinuria are summarized in Table 1. Nephrotic syndrome is usually due to glomerular diseases.

In the presence of proteinuria and hypertension, it is not always clear whether or not preeclampsia is present. Moreover, women with renal disease are more likely to develop superimposed preeclampsia. To help distinguish preeclampsia, a thorough longitudinal history (see 'Questionnaire' in Table 2), maternal and fetal preeclampsia work-up⁷ (elevated liver enzymes are suggestive of preeclampsia) and biologic markers of disease (e.g. dsDNA titers) may be helpful. Occasionally, a renal biopsy is necessary. This complex situation mandates close follow-up, especially when remote from term and when expectant management is applied, as delivery is the cure of preeclampsia, but not for GN. Sometimes it may be impossible to make the distinction until after delivery. For women with pre-existing renal disease or a high risk of preeclampsia, baseline preeclampsia work-up⁷ in the first trimester (or at first visit if later) is extremely important and useful to aid accurate diagnosis of the clinically dominant lesion later in pregnancy. There is abundant literature on the evaluation and

Table 1 Causes of proteinuria

Glomerular diseases

- Preeclampsia*
- Diabetes (type 1 and 2)[†]
- IgA GN[‡]
- Focal and segmental glomerulosclerosis (FSGS) (primary and secondary)[†]
- Lupus nephritis
- Infection-related GN (e.g. HIV, hepatitis B and C, poststreptococcal, visceral abscess, endocarditis, other)
- Drug-related GN
- Other glomerular diseases in young women: minimal change, membranous GN, membranoproliferative GN, other rare glomerular diseases (e.g. amyloidosis, Fabry, Alport)

Other causes of proteinuria[‡]

- Renal diseases: reflux nephropathy, congenital anomalies, polycystic kidney disease, interstitial nephritis
- Transient causes: exercise, fever and sepsis, congestive cardiac diseases, subarachnoid haemorrhage (SAH) and intracranial haemorrhage, seizures
- Non-renal causes: urinary tract infection, contamination (e.g. vaginal bleeding)

GN, glomerulonephritis; IgA, immunoglobulin A

*Most frequent cause of nephrotic syndrome in pregnancy

[†]Frequent causes in pregnancy; prevalence will vary according to geographic location

[‡]Rarely or not causing nephrotic range proteinuria

Table 2 Assessment of nephrotic range proteinuria

Questionnaire

- Birth weight, history of prematurity and perinatal complications
- Infancy and childhood: urinary tract infections and vesicoureteral reflux, nocturia, previous urinary tract investigations, childhood GN (postinfectious GN, Henoch–Schönlein purpura, minimal change disease)
- Familial history of renal diseases
- Current or recent symptoms: oedema (onset, progression), urinary symptoms (frothy urine, haematuria), systemic symptoms, in particular suggestive of SLE, infectious symptoms and risk factors for HIV/viral hepatitis
- Drugs (prescription, over the counter, recreational)

Physical examination

- Vitals: blood pressure (BP), heart rate, weight, input/output, fluid balance
- Look for puffy eyelids, presence or absence of jugular vein distension, lungs (pleural effusion), ascites (more difficult with gravid uterus), presacral oedema, lower limb (severe oedema and signs of deep vein thrombosis), other stigma of systemic diseases

Baseline work-up

- Urine analysis and culture, urine sediment (also obtain previous results)
- Quantification of nephrotic range proteinuria
 - Urinary dipstick: easy to perform for detection of proteinuria but results vary according to urine concentration; not good for quantification
 - Urinary spot (protein/creatinine ratio, albumin/creatinine ratio): easy to perform and repeat but less reliable at high range proteinuria; methods and units differ according to local laboratories
 - 24 hours urine collection: inconvenient and may be inaccurate when incomplete²³
- Blood work: FBC, creatinine, Na, K, Cl, albumin, glucose (of note: cholesterol will be increased in pregnancy)

Preeclampsia work-up as per guidelines¹²

Additional investigations as indicated:

- Renal ultrasound
- Bicarbonate, Mg, Ca, PO₄, PTH, urea, uric acid, HbA1c
- C-reactive protein, sedimentation rate, C3, C4, ANA, viral serology (hepatitis B, C, HIV), ANCA, anti-GBM, ASLO
- Renal biopsy: when diagnosis is needed for *de novo* nephrotic syndrome (not preeclampsia), especially for initiation of treatment with immunosuppressive drugs during pregnancy; decision according to gestational age, clinic and balance of risks of procedure (not really increased by pregnancy but influence on consequences and treatment of renal haematoma) and maternal–fetal risks/benefits ratio of diagnosis

GN, glomerulonephritis; SLE, systemic lupus erythematosus; FBC, full blood count; PTH, parathyroid hormone; HbA1c, glycated haemoglobin; ANA, antinuclear antibodies; ANCA antineutrophil cytoplasmic antibodies; Anti-GBM, anti-glomerular basement membrane (GBM) antibody; ASLO, anti-streptolysine O antibody

management of preeclampsia (nephrotic syndrome being part of the spectrum) and we refer the reader to consult specific preeclampsia guidelines.⁷

Assessment of nephrotic syndrome

In order to investigate nephrotic syndrome, a focused questionnaire and physical examination of the pregnant woman and investigations are performed (Table 2). For quantification of proteinuria, we use at our centre the spot protein/creatinine ratio for baseline work-up and longitudinal follow-up. According to our local laboratory, a ratio of >3 g/g is consistent with nephrotic range proteinuria. Some centres use 24 hours protein (and creatinine) to confirm nephrotic range proteinuria (>3 g/day) when the spot protein/creatinine ratio is above 230 mg/mmol.

Nephritic syndrome (defined as haematuria ± red cell casts, proteinuria, oedema, hypertension and acute kidney injury)

requires an urgent referral to nephrology, whereas *de novo* nephrotic syndrome (where preeclampsia has been ruled out) should be assessed by or discussed with nephrology in most cases, depending on local expertise and facilities.

IMPACT OF NEPHROTIC SYNDROME IN PREGNANCY

Maternal and fetal considerations

Increased proteinuria (even severe), in the absence of renal impairment or hypertension, is usually associated with a good maternal and fetal prognosis overall. However, more complications may occur when proteinuria is not isolated. Renal insufficiency is associated with an increased risk of further deterioration of renal function (and end-stage renal disease if severe) as well as hypertension and preeclampsia. The presence of pre-existing hypertension carries additional maternal and fetal risks of complications such as severe preeclampsia. Intrinsic renal disease characteristics and prognosis, as well as concomitant maternal comorbidities, need to be considered in the balance of risks. Fetal complications include growth restriction, prematurity, fetal loss, fetal anasarca and polyhydramnios. In nephrotic syndrome, fetal growth restriction is most likely related to reduced utero-placental perfusion consequent upon low colloid osmotic pressure and reduction in effective blood volume. Genetic transmission of hereditary nephrotic syndrome is rare (e.g. minimal change, focal segmental glomerular sclerosis or membranous GN) and needs to be discussed if appropriate.

Preconception counselling

A woman with nephrotic syndrome before pregnancy should have her disease controlled before planning a pregnancy, aiming for remission to be attained whenever possible. Not only proteinuria, but also blood pressure and renal function should be optimized.

Women should be counselled specifically regarding their medications. The small risks of congenital malformations after first trimester exposure⁸ to the antiproteinuric drugs (angiotensin-converting enzyme inhibitors [ACEIs] and angiotensin-receptor blockers [ARBs]) should be explained. Many nephrologists will opt to continue these agents until conception for renoprotection. ACEIs and ARBs should be discontinued as soon as pregnancy is confirmed. However, it is important to realize that proteinuria is likely to increase thereafter due to the combination of drug cessation and physiological changes of pregnancy (in our experience, often more than double).

Statins are routinely stopped before or at conception. Furosemide and thiazides are not known teratogens. Less information is available on the use of amiloride, a potassium-sparing diuretic; however, its use may be justified. The use of immunosuppressive drugs need to be re-evaluated when contemplating a pregnancy and the dose adjusted to the lowest possible level or switched to another agent when necessary. For instance, azathioprine, cyclosporine and tacrolimus can be used in pregnancy, whereas mycophenolate mofetil (MMF) is contraindicated. Finally, we recommend the addition of low-dose aspirin to reduce the risk of preeclampsia, acknowledging that few women with underlying renal disease were enrolled in the trials that showed the benefit of aspirin in preeclampsia prophylaxis.⁹

MANAGEMENT CHALLENGES DURING PREGNANCY

Nephrotic syndrome may be challenging for the pregnant woman and care-givers. In this section, we present maternal clinical issues and some suggestions for monitoring. Proteinuric diseases are not all the same. For instance, severe nephrotic proteinuria does not always cause severe clinical manifestations, and modest nephrotic proteinuria may be very symptomatic. A multidisciplinary team is needed, including nephrologist, obstetric medicine specialist, obstetrician, maternal-fetal medicine specialist, neonatologist, dietician, nurses and midwives. Appropriate treatments, including immunosuppressive drugs should not be withheld during pregnancy if deemed necessary for control of maternal disease. Fetal surveillance and management (e.g. corticosteroids for fetal lung maturation) needs to be carried out according to the attending obstetrician/MFM specialist and periodic discussion is of utmost importance for the wellbeing of both mother and baby. The frequency of the clinical and laboratory monitoring needs to be individualized and will be adjusted according to clinical assessment, evolution, severity and prognosis of the underlying renal disease, gestational age and ongoing treatments (e.g. every 2 weeks, weekly or daily).

Clinical issues (see Table 3)

Oedema

Renal water and salt retention combined with interstitial fluid leak due to decreased oncotic pressure lead to peripheral oedema. Most of the time, oedema is easily managed by conservative measures. However, in severe nephrotic syndrome, peripheral oedema and anasarca (extreme generalized oedema) may lead to great discomfort and significant related problems, such as difficulties for the pregnant woman to ambulate, oozing blisters and secondary skin complications (such as infection), severe genital oedema, shortness of breath secondary to pleural effusion, increased risk of non-cardiogenic pulmonary oedema (usually precipitated by an additional risk factor such as intravenous fluid administration during labour, medication or sepsis), difficulty with regional anaesthesia because of lumbar oedema, or postoperative complications from leaking wound after caesarean section.

Strategies:

- Stockings (special attention to well-adjusted leg stockings, to prevent secondary venous stasis and skin wounds);

Table 3 Clinical issues in the management of nephrotic syndrome in pregnancy*

Oedema
Blood pressure control
Acute kidney injury
Thrombotic risk
Anaemia
Malnutrition
Vitamin D deficiency
Risk of infection
Timing of delivery
Avoidance of non-steroidal anti-inflammatory drugs

*In the management of nephrotic syndrome not as a result of preeclampsia

- Leg elevation for comfort and promote venous return (prolonged recumbent position however, will increase thigh, back and abdominal oedema);
- Salt restriction <100 mmol/day (2.3 g of sodium);
- Water restriction (around 1.5 L/day);
- Diuretics: furosemide (oral or intravenous): start with lower dose 5–10 mg (to prevent acute intravascular dehydration and hypotension – see below for monitoring) and titrate according to clinical response (diureses, weight, blood pressure [BP]); thiazide may be added if there is resistance to loop diuretic; we usually aim at a negative balance of no more than 0.5–1.0 L per day to prevent complications.
- Colloids: The use of intravenous albumin to improve intravascular oncotic pressure remains controversial;¹⁰ some use intravenous albumin for hypotension and rising serum creatinine but the effects are always transient; there is no indication to use intravenous albumin to increase serum albumin levels; recent data on other colloids (e.g. hetastarch, HES) in pregnancy are mainly for the prevention or treatment of hypotension induced by spinal anaesthesia. We do not advocate their use other than in exceptional circumstances.

Monitoring:

- Daily weight and input/output, BP and heart rate when adjusting treatment;
- Metabolic disturbances: electrolytes (sodium, potassium, magnesium, calcium), check for diuretic-induced alkalosis (normal bicarbonate levels in pregnancy around 18–20 meq/L);
- Renal function: serum creatinine and urea; $\pm$ 24 hour creatinine clearance (see below);
- Twenty-four hour urinary sodium excretion may be useful to assess resistance to diuretics (aim for sodium excretion >100 mmol/day [2.3 g/day]).

Blood pressure control

BP may be elevated, normal or low in nephrotic syndrome, according to the underlying cause and other medical comorbidities. In proteinuric renal diseases outside pregnancy, the target blood pressure <130/80 mmHg to decrease proteinuria and renal damage.¹¹ In pregnancy, one needs to balance maternal BP and uteroplacental blood flow, taking into account fetal wellbeing. Although there is concern regarding decreased fetal growth when blood pressure is too low in hypertensive pregnancies,¹² there are to our knowledge no reliable data in nephrotic syndrome. Although controversial, we extrapolate from outside pregnancy and usually aim for a BP of $\leq$ 130/80 mmHg in severe nephrotic syndrome, trying to avoid lowering BP too much with antihypertensive treatment (<110/70 mmHg) in the face of a reduced effective blood volume. Others aim for a BP of 110–140/80–90 mmHg. Again, BP goal needs to be individualized according to clinical and pre-pregnancy renal history.

Strategies:

- Salt restriction/water restriction/diuretics (see above) when hypervolemia is present;
- Antihypertensive drugs in pregnancy: see Table 4.

Table 4 Antihypertensive drugs in nephrotic range proteinuria during pregnancy

- Diltiazem: use to decrease proteinuria outside pregnancy; very small study in pregnant women with renal disease ($n = 7$);²⁴ good choice in 2nd–3rd trimester (caution in first trimester as safety not yet established). Avoid concomitant use with beta-blockers
- Labetalol: often used in pregnancy, easy to titrate; other beta-blockers (avoid atenolol)
- Methyldopa: often used in pregnancy; if already anaemic, beware of haemolytic anaemia and warm antibodies
- Nifedipine: outside pregnancy, not first choice in proteinuric renal disease as dihydropyridine calcium channel blockers may increase proteinuria by preferential dilation of afferent arteriole; however, remain an alternative when needed for BP control; often used in proteinuric preeclampsia
- Hydralazine and other^{7,17,18}

BP = blood pressure

Acute kidney injury

Acute kidney injury (AKI) (new onset or superimposed on chronic kidney disease [CKD]) can be approached in pregnancy by looking at prerenal, renal and postrenal causes, and investigation carried out appropriately. The main reason for AKI in nephrotic syndrome is prerenal due to low intravascular oncotic pressure.

To assess renal function in pregnancy, serum creatinine is used as a marker of GFR.¹³ However, it needs to be remembered that in pregnancy, serum creatinine first decreases during the first and second trimester (<70 μ mol/L) (0.79 mg/dL) to increase during the third trimester near term (<80 μ mol/L) (0.90 mg/dL).⁵ Twenty-four hour urine collections are less often used to evaluate creatinine clearance. Formulas for estimated GFR (eGFR) or creatinine clearance (e.g. modification of diet in renal disease [MDRD], Cockcroft–Gault) have not been validated for pregnant women or in AKI.

- Prerenal: decreased oncotic pressure, over-aggressive use of diuretics, especially when strict water and salt restrictions are applied (be careful with in-hospital versus outpatient modification in lifestyle and intake). Other potential causes in pregnancy include diarrhoea, nausea and vomiting, infection and sepsis;
- Renal: underlying renal disease progression, preeclampsia, acute tubular necrosis, acute interstitial nephritis, others;
- Postrenal: ureteral compression from gravid uterus, especially in multiple pregnancy or polyhydramnios.

Thrombotic risk

As well as the physiological changes of haemostatic factors leading to a prothrombotic state in pregnancy, the risk of thrombosis is increased further in nephrotic syndrome due to several factors. These include: increased urinary loss of anticoagulant proteins (such as antithrombin), increased hepatic synthesis of clotting factors, some degree of intravascular hypovolemia (interstitial fluid leak, and a combination of salt/water restriction and use of diuretics), inflammation as well as decreased mobilization due to peripheral oedema and discomfort.

Other predisposing conditions (e.g. known thrombophilia) and additional risk factors (e.g. obesity, immobilization due to obstetric conditions) also need to be taken into account. In

our opinion, nephrotic range proteinuria *per se* is not a reason to screen for underlying thrombophilia unless clinically indicated by history. Classic sites of occurrence of thrombosis include the renal veins, the lower legs (left > right), with more proximal and extensive involvement of the iliac veins up to the vena cava, with the feared complication of pulmonary embolism.

Although there is consensus that thromboprophylaxis is warranted in a high-risk situation, the threshold to initiate such prophylaxis in nephrotic syndrome is still a matter of debate. Some will go according to urinary proteinuria (>3–3.5 g/day) or antithrombin levels (below normal) or serum albumin levels (<20–25 g/L). The rationale for using a serum albumin level <20 g/L comes from the membranous GN literature in the general population where increased risk of thromboembolic event was observed for lower levels of albuminaemia.

The choice of anticoagulant agent and dosing regimens are the same as for other medical conditions, including low-molecular-weight heparin (LMWH) (unless severe renal function impairment with an eGFR < 30 mL/minute) or unfractionated heparin (UFH). One needs to consider side-effects of treatment as well as the usual issues, especially around delivery, such as risk of bleeding and the need for regional anaesthesia or caesarean section. The level of anticoagulation (prophylactic versus intermediate versus therapeutic) also needs to be individualized according to the risk of thromboembolic events.^{14,15}

In our practice, we usually offer heparin prophylaxis in pregnancy when serum albumin is <25 g/L or sooner when there are risk factors in addition to the nephrotic syndrome. We adjust the level (prophylactic or intermediate) according to perceived total risk and use body weight (an estimate of the current weight without oedema excess) to adjust the daily dosage of heparin. Except for special circumstances, we do not monitor anti-Xa levels or activated partial thromboplastin time (aPTT).

Anaemia

The physiological anaemia of pregnancy may be exacerbated by a combination of causes, and appropriate anaemia work-up is needed (Table 5). Supplements of iron, vitamin B₁₂ and folate to promote reticulocytosis should be prescribed when appropriate. With nephrotic syndrome, intravenous iron is more likely to

be needed due to a combination of decreased absorption, decreased GFR and iron sequestration. When iron loading is needed, we use intravenous iron sucrose, 200 mg/dose administered over several days (total dose approximated using the formula: [Prepregnancy weight (kg) × (Target haemoglobin [g/L] – Actual haemoglobin) × 0.24 + 500 mg].¹⁶ Recombinant EPO may be needed in women with CKD.

Nutrition

In pregnancy, there is an increased nutritional need in order to sustain fetal and placental growth, and maternal metabolism. Malnutrition may occur in nephrotic syndrome when there is significant urinary loss of protein and other nutrients and/or decreased intestinal absorption secondary to intestinal wall oedema. The inflammation secondary to some renal GN may also contribute to increased maternal catabolism. With excess oedema, monitoring weight gain in pregnancy as a surrogate of nutritional status may be misleading. Therefore, the diligent evaluation of intake and nutritional needs from the dietitian is crucial in this situation. Parenteral nutrition is an unproven intervention and is discouraged due to the risks inherent to its invasiveness.

Vitamin D deficiency

Besides the high prevalence of underlying vitamin D deficiency reported in pregnancy, the increased need in pregnancy combined with increased urinary loss of vitamin D may lead to severe deficiency.

Various regimens for vitamin D supplementation are suggested for repletion in pregnancy, some with high-dose vitamin D to quickly replenish maternal storage. In nephrotic syndrome, we begin with 5000–10,000 IU per day for 2–4 weeks for severe deficiency (level <30) with a maintenance dose of 1000 IU per day thereafter to account for urinary losses, and adjust according to repeat calcium and vitamin D serum levels (at least monthly).

Along with vitamin D, adequate calcium intake (diet and/or supplements) should be evaluated (reminder: total calcium needs correction for decreased albumin level or measure ionized calcium).

Risk of infection

The increased urinary loss of gammaglobulins is known to be associated with increased risk of infection in patients with nephrotic syndrome. However, we were unable to find more information on this incremental risk in pregnancy. Therefore, we suggest close surveillance for symptoms of infection and prompt investigation and appropriate treatment when indicated. In our opinion, there is no need for antibiotic prophylaxis unless indicated by a clinical condition (e.g. recurrent urinary tract infection [UTI]) or by high levels of immunosuppressive drugs (e.g. in active lupus nephritis). Vaccination also needs to be updated and influenza vaccine has to be given in season.

When to deliver?

As in other medical situations in pregnancy, the decision needs to be individualized and following multidisciplinary discussion

Table 5 Anaemia in nephrotic syndrome

Contributing causes

- Physiological anaemia of pregnancy
- Inflammation of acute and/or chronic disease
- Decreased intestinal absorption of iron, B₁₂ and folate
- Renal loss of transferrin
- Decreased erythropoietin production if GFR significantly decreased (usually <50 mL/minute)
- Gastrointestinal loss and other sources of bleeding

Baseline work-up

- Blood smear, reticulocytes
- Iron stores (total iron, saturation, ferritin)
- Vitamin B₁₂, folate
- Inflammation markers (C-reactive protein, sedimentation rate)
- Erythropoietin level when GFR <50 mL/minute
- Haemolysis tests (haptoglobin, LDH, unconjugated bilirubin)
- Haemoglobinopathies screen (haemoglobin electrophoresis)

GFR, glomerular filtration rate; LDH, lactate dehydrogenase

considering the gestational age, maternal/fetal current well-being and prognosis, risks of complications from continuing the pregnancy versus risks of complications of early delivery. Deteriorating renal function over weeks/months or an abrupt deterioration that may not recover or may even worsen after delivery or the need for renal replacement therapy may also prompt early delivery. Although the level of proteinuria *per se* is not considered an indication for delivery, uncontrolled severe oedema/anasarca with significant complications non-responsive to medical approaches or inability to monitor blood pressure, or gain venous access would also be considered indications for delivery. Preeclampsia or uncontrolled hypertension are well-recognized indications for delivery because of the potential for severe maternal and fetal morbidities and mortality. Most would also agree that once term is achieved (>37 weeks) or when the risks from fetal prematurity are deemed low according to assessment and local expertise, delivery could be considered to lessen serious maternal risks. Finally, any worrisome fetal complications (the most common being slowing of fetal growth) or other significant obstetric conditions may prompt delivery. Decision of mode of delivery should be based on usual obstetric indications.

POSTPARTUM MANAGEMENT

After delivery, pregnancy-induced physiological changes will return back to the prepregnancy state over hours, days and months. However, care-givers need to beware of preeclampsia occurring postpartum, of possible renal function deterioration and postpartum rises in blood pressure. Therefore, close maternal surveillance (both clinical and laboratory) remains important.

Depending on the aetiology, nephrotic syndrome may improve rapidly or it may take more than the usual six weeks to resolve, implying the need for longer postpartum follow-up. Completion of the renal work-up should be undertaken if indicated (e.g. renal biopsy) and referral to nephrology for long-term management should be considered.

After delivery, once there is no longer concern of fetal exposure to drugs, other treatments for nephrotic syndrome can be considered, and more optimal or appropriate treatment be resumed or started if needed (e.g. ACEIs/ARBs, statins, immunosuppressive drugs such as MMF). However, another important consideration is the woman's desire to breastfeed and safety of drugs for the newborn. Again, risks and benefits of taking versus withholding a drug, and alternatives during the postpartum period, should be discussed. This is an area of constant change as more information on drugs and breastfeeding become available. Several specialized sources can be consulted for updated information (e.g. www.toxnet.nlm.nih.gov, and see refs 17 and 18).

Clinical issues

Avoid non-steroidal anti-inflammatory drugs

When there is significant oedema, oliguria, AKI/CKD or hypertension, it is of utmost importance to avoid non-steroidal anti-inflammatory drugs (NSAIDs) for postpartum analgesia. These are routinely prescribed in most postpartum units, with often patient-self administration and hence vigilance is needed.

NSAIDs inhibit prostaglandins leading to altered renal haemodynamic, which promote water and salt retention and

secondary hypertension,¹⁹ and significantly increase the risk of AKI in nephrotic syndrome and renal disease.

Oedema

Look for spontaneous postpartum diuresis that can amount to several litres per day, with rapid improvement of oedema and serum albumin levels. Conservative measures (stockings, leg elevation) may be applied as needed. The indication for salt and water restriction, as well as diuretics should be re-evaluated on a daily basis. Diuretics are not contraindicated with breastfeeding, although there are concerns with milk production if dehydration occurs.

Blood pressure control

The goal postpartum is strict BP control, meaning <130/80 mmHg at the hospital/clinic and <125/75 mmHg at home. First choices to decrease proteinuria are ACEIs or ARBs if no contraindications (e.g. AKI, breastfeeding a preterm/small baby, consult with a neonatologist). Several ACEIs are now considered compatible with breastfeeding (e.g. captopril,²⁰ enalapril²¹). The aldosterone antagonist spironolactone is also popular in proteinuric disease and is considered compatible with breastfeeding by the American Association of Pediatrics.²² Additional antihypertensives used during pregnancy can be prescribed as needed in a breastfeeding mother. Non-dihydropyridine calcium channel blockers (e.g. verapamil) may be preferred over dihydropyridine calcium channel blockers because of their antiproteinuric effects.

Acute kidney injury

Renal function may transiently deteriorate in the peripartum/postpartum period, but most will recover after days or weeks. The postpartum renal prognosis will depend on several factors, such as the cause and severity of the underlying renal disease and timing of appropriate treatment. Prompt management is required to avoid reaching non-reversible or severe or end-stage renal disease. Even small decrements in renal function will have long-term implications for dialysis-free survival.

Thromboprophylaxis

The postpartum period remains a high-risk time for thromboembolic disease. Therefore, initiation or continuation of prophylactic treatment needs to be considered. Options include LMWH, UFH or warfarin (all compatible with breastfeeding) and we consider a postpartum duration of six weeks as with other high-risk situations, especially following caesarean section, bed rest or other risk factors.¹⁵ Longer duration may be required if severe nephrotic syndrome persists according to practices outside pregnancy.

CONCLUSION

In summary, nephrotic syndrome in pregnancy is associated with challenges for clinicians. In this review, we have attempted to provide a practical approach to the evaluation, management and monitoring of oedema and anasarca, blood pressure control, acute kidney injury and a reminder to also consider

thrombotic and infection risks, as well as anaemia and nutritional issues. Appropriate evaluation of the underlying renal disease and its specific treatments remains of utmost importance, and a multidisciplinary approach is necessary to optimize both maternal and fetal care and outcomes.

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