Glomerular diseases in pregnancy: pragmatic recommendations for clinical management

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Our understanding of the various aspects of pregnancy in women with kidney diseases has significantly improved in the last decades. Nevertheless, little is known about specific kidney diseases. Glomerular diseases are not only a frequent cause of chronic kidney disease in young women, but combine many challenges in pregnancy: immunologic diseases, hypertension, proteinuria, and kidney tissue

damage. An international working group undertook the review of available current literature and elicited expert opinions on glomerular diseases in pregnancy with the aim to provide pragmatic information for nephrologists according to the present state-of-the-art knowledge. This work also highlights areas of clinical uncertainty and emphasizes the need for further collaborative studies to improve maternal and fetal health.

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Women with various chronic diseases often consider successful pregnancy as a demonstration of having regained a "normal" life. This applies to women with chronic kidney diseases (CKDs)[1,2] and particularly to those with glomerular diseases (GDs).

Clinical approaches toward pregnancy in the setting of kidney diseases have changed in the last few decades. Pregnancy in this population was previously discouraged because of concern over maternal complications and unfavorable fetal outcomes. A significant driver of this change has been the progress in perinatal care and the management of pregnancy in patients with advanced CKD, and those on dialysis.[3]

However, the acknowledgement of the importance of even minor kidney involvement before, or during, pregnancy, including kidney stones, previous episodes of acute kidney injury, kidney donation, or GD even in remission, has broadened the definition of "high-risk pregnancies."[4–6]

Although evidence as to the importance of kidney function and of kidney adaptation to pregnancy is increasing, little is known about specific kidney diseases. GDs, which frequently affect young patients, are particularly relevant in this context. Autoimmune-mediated GDs may be affected by the hormonal milieu in many pregnancies, the prototype of this being lupus nephritis (LN). GDs may also appear, be initially diagnosed, or flare during pregnancy, and subsequent therapy is often limited by the actual risk or concern for fetal toxicity.

An international working group undertook a review of the current literature and expert opinion on GDs in pregnancy with the aim to provide pragmatic information for nephrologists, helpful particularly for the preconception counseling of patients, while highlighting areas of clinical uncertainty and debate.

EPIDEMIOLOGY: WHAT ARE WE TALKING ABOUT?

Robust data defining the prevalence and type of GDs in pregnancy are not available. This is mainly due to variations in capturing and reporting of data on GDs in pregnancy[7,8] and the heterogeneity in the study populations and types of studies. There is also a lack of routine kidney function testing in pregnancy, thus limiting detection of GD in pregnancy. With these caveats in mind, GDs identified before or during pregnancy are likely to be underestimated, particularly in low- to middle-income countries, where kidney function testing may be limited, although CKD prevalence is high.[9–11]

General population data indicate that 3% to 6% of women of child-bearing age have CKD[9], up to 3% of women with CKD are of child-bearing age,[12] and up to 3.3% of pregnant women have laboratory evidence of CKD.[13] In an Australian study, 0.3% of pregnant women had a kidney diagnostic code, but only 0.01% had an identified immunologic disease or GD,[14] likely reflecting poor identification of GD in pregnancy.

Early GD may influence pregnancy outcomes but can be missed in pregnancy and only diagnosed later in life. A study of Norwegian women who had a kidney biopsy at any time after their last pregnancy found that those who had a history of preterm birth or preeclampsia had higher rates of focal segmental glomerular sclerosis (FSGS), crescentic glomerulonephritis, or anti-neutrophil cytoplasm antibody vasculitis, compared with women who had a normal pregnancy.[15] A high prevalence of GD in preeclamptic patients likewise was recently reported in Denmark[16] and Italy.[17] Preeclampsia may be the first sign of a GD, usually diagnosed in the first few years postpartum, or it may represent one hit in a multiple-hit pathogenesis of a GD diagnosed later in life.

Among the GDs diagnosed by kidney biopsies in pregnancy or in the postpartum period, the most common ones are FSGS, IgA nephropathy (IgAN), and LN.[18,19] Other GDs are rare, but most of them have been reported in pregnancy.[16]

Much more is known about the prevalence of GDs in pregnant women on renal replacement therapy: 35% to 56% of women on chronic dialysis or those having received a kidney transplant have a GD as their primary renal disease.[20,21]

TOOLS FOR THE DIAGNOSIS AND MONITORING OF GDs IN PREGNANCY

In patients with a GD, as for any pregnancy, the urinary tract undergoes substantial hemodynamic adaptations during gestation.[22] These changes (Supplemental Table S1) include a decrease in kidney vascular resistance, an increase in kidney blood flow, and a concomitant increase in glomerular filtration rate (38%–56% increase in creatinine clearance[23]), by the first trimester of pregnancy.

There is currently no widely accepted formula for the estimation of kidney function in pregnancy. Some authors consider urinary creatinine clearance as the gold standard[24]—and adding 24-hour urine collection allows for a better assessment of proteinuria. Others recommend evaluating kidney function using serum creatinine concentration and suggest that serum creatinine concentration >85% (76 μmol/L), 80% (72 μmol/L), and 86% (77 μmol/L) of the nonpregnant upper limit of normal in the first, second, and third trimester, respectively, should be considered abnormal in pregnancy[25,26] (Supplemental Table S2).

Staging of CKD in pregnant patients with a GD should be based on prepregnancy values, whenever possible.[25] The absence of an early decrease in serum creatinine during pregnancy compared with prepregnancy concentrations has been proposed as a poor prognostic marker of renal function outcome.[27] Glomerular hyperfiltration, however, has not been associated consistently with better pregnancy-related outcomes, at least during the early stages of CKD.[28] Longitudinal kidney function (e.g., decrease of estimated glomerular filtration rate in midterm) in pregnancy may be as relevant as the baseline absolute values.[29–31]

As with estimated glomerular filtration rate estimations, there is no consensus regarding the best method for assessing proteinuria in pregnancy. Use of the spot urinary protein-to-creatinine ratio (UPCR) is usually preferred to timed urine collections because of the possibility of underestimation,[32] variability,[33] and inconvenience, and the potential for treatment delay with the latter. The UPCR is practical for screening for hypertensive disorders of pregnancy, for which new onset of proteinuria (UPCR >30 mg/mmol) is still one discriminating parameter between preeclampsia and gestational hypertension. The limitations of spot UPCR or urinary albumin-to-creatinine ratio are well acknowledged. The recently proposed option of calculating the UPCR and/or urinary albumin-to-creatinine ratio from a 16- to a 24-hour urine collection may be utilized in pregnant patients with GDs.[34] The approach balances the advantages of a 24-hour urine collection with the practical constraints of this test (Supplemental Table S1).[34]

Considering the limitations of the indirect methods, and the advantages of a precise quantification of kidney function and of proteinuria in pregnancy, a working compromise would be to rely, when feasible, on the gold standard, based on 24-hour urine collection, while acknowledging that in some cases surrogate estimations of kidney function (estimated glomerular filtration rate, serum creatinine, and trends in UPCR, if possible, on extended-hour urine collections) provide reliable information for the clinical management of patients.

Similarly, what represents a significant increase in proteinuria during pregnancy in women with a preexisting GD has not been established; doubling of proteinuria compared with prepregnancy values has been previously used in research cohorts.[5,35,36]

RISK EVALUATION FOR PREGNANCY, THE WOMAN, AND THE FETUS IN PATIENTS WITH A KNOWN GD

Three major determinants of pregnancy-related outcomes are identified: kidney function impairment—the most extensively studied and probably the most important factor—proteinuria, and hypertension.[5,37] Their effects are most likely also modulated by the type of kidney disease.

Little is known regarding the effects that different types of GDs have on pregnancy outcomes. This is probably mainly due to their heterogeneity. Pregnancy outcomes have been more extensively studied in the most common GDs (namely, IgAN or LN), but the general aspects of management probably apply to all types of GDs.[5] The main pregnancy-associated adverse events associated with CKD, including GDs, are summarized in Supplemental Table S3.

Several studies have assessed pregnancy outcomes in women with GDs, including pregnancies that occurred between the 1960s and late 1990s. The findings of these studies may not reflect the current risks, as they do not consider the marked improvements in the management of pregnancy and of GDs.

As for maternofetal outcomes excluding kidney function, GDs generally seem to be associated with a higher risk of adverse pregnancy events compared with patients with other types of kidney diseases. This increased risk even applies to women with a GD and CKD stage 1, mild proteinuria (<1 g/24 h), or normal blood pressure (i.e., a GD in complete clinical remission). Pregnancy outcomes in these patients are similar to those of women with kidney transplantation.[5,38]

Conversely, with respect to kidney function, women with a GD and normal kidney function before pregnancy do not have a clearly increased risk of kidney function impairment during or after pregnancy, even in the long-term, compared with nonpregnant women with a GD. This finding has been documented particularly in women with IgAN[39,40] and LN.[41,42]

How should women with GD and CKD starting a pregnancy be monitored?

The frequency of kidney function testing is not clearly established in pregnant women with a GD. A flowchart adapted from recent recommendations from the Italian Study Group on Kidney and Pregnancy[43] is shown in Figure 1.

One critical point is how to distinguish GD worsening from preeclampsia. This differential diagnosis is particularly challenging because of the heterogeneity of preeclampsia and its frequent association with all kidney diseases, including GD.[44–47] Recent evidence linking preeclampsia to an angiogenic-antiangiogenic imbalance[48] has led to the clinical use of various biomarkers to predict the occurrence of preeclampsia.[49] The measurement of the soluble fms-like tyrosine kinase 1/placental growth factor ratio is increasingly being recommended, but its cost-effectiveness remains to be fully assessed.[50] A limited number of studies have assessed the soluble fms-like tyrosine kinase 1/placental growth factor ratio in pregnant women with CKD of various causes. This ratio is generally within the normal range in cases of pure worsening of preexistent CKD but is increased in the case of preeclampsia.[51,52] The interpretation of an alteration in the soluble fms-like tyrosine kinase 1/placental growth factor ratio should be made with caution, as preeclampsia may be superimposed on CKD. The levels are usually intermediate in this setting, but this finding is nonspecific.[52–54] Low placental

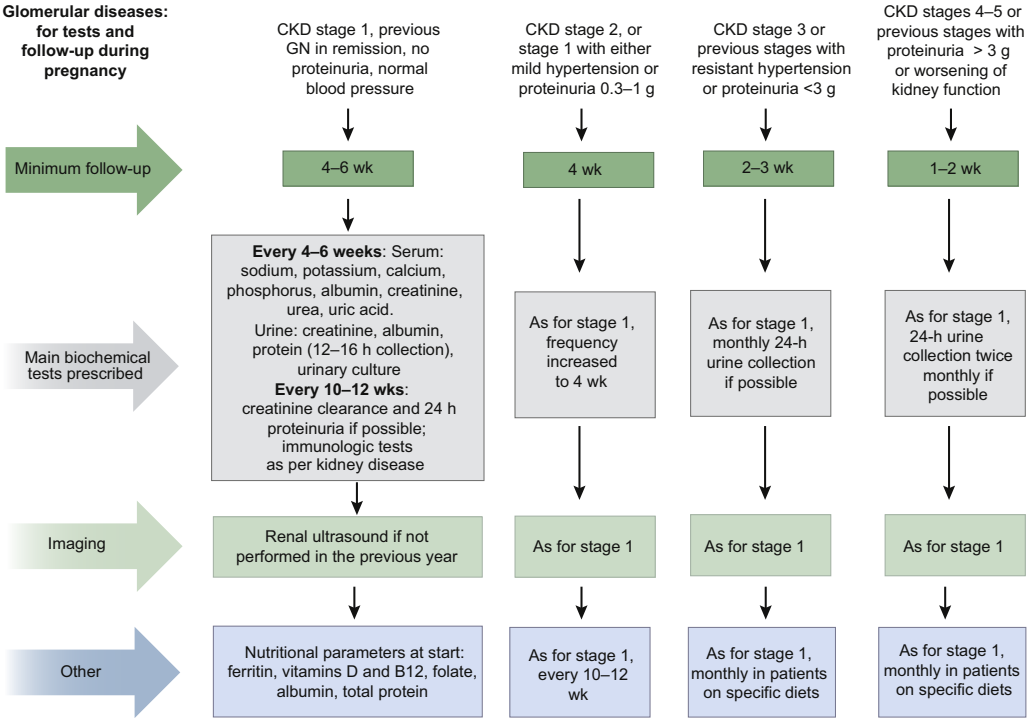

Figure 1 | Proposed follow-up of patients with glomerular disease (GD) during pregnancy. CKD, chronic kidney disease.

growth factor concentrations in isolation also have predictive and diagnostic utility in preeclampsia, and cost-effectiveness has been shown in general obstetric cohorts.[55,56] The threshold for distinguishing preeclampsia is, however, higher in women with CKD, with the clinical manifestation of preeclampsia hypothesised to occur at lower levels of placental dysfunction when the endothelium is primed by CKD.[36]

Severely impaired uteroplacental Doppler flows also indicate placental involvement, commonly associated with intrauterine growth restriction, whereas worsening of kidney disease is usually associated, in the absence of hypertension, with preserved fetal growth.[43]

The simplest and perhaps most simplistic way to make a differential diagnosis between preeclampsia and GD after delivery is based on the persistence of proteinuria and hypertension beyond 3 months postpartum. The absence of proteinuria, however, does not fully rule it out.

DIAGNOSTIC ISSUES IN PATIENTS WITH *DE NOVO* GD, WITH PARTICULAR EMPHASIS ON KIDNEY BIOPSY

Three distinct situations may be encountered during pregnancy in women with no history of GD who present with renal function abnormalities suggestive of GD: (i) detection of proteinuria and/or hematuria with preserved kidney function, (ii) diagnosis of nephrotic syndrome, and (iii) occurrence of subacute or acute kidney injury with proteinuria or nephrotic syndrome.

The diagnostic approach to these 3 situations is summarized in Figure 2.

No clear definition of nephrotic syndrome in pregnancy, particularly the degree of hypoalbuminemia, exists. As serum albumin gradually decreases from the beginning of pregnancy (mainly due to hyperhydration),[57] we suggest the use of a modified definition of nephrotic syndrome, whereby serum albumin below the lower limit of normal for gestational age (Supplemental Table S2)[57] and proteinuria >3 g/d are suggestive of nephrotic syndrome. Severe nephrotic syndrome would be defined by a serum albumin <50% of the lower limit of normal.

The workup of a patient with nephrotic syndrome and/or subacute/acute kidney injury aims to predict the underlying kidney disease and, thus, start probabilistic treatment, based on patient history, clinical status (presence of extrarenal manifestations suggestive of systemic disorders), and biological tests (mainly autoantibodies and complement assays; Supplemental Tables S4 and S5). Kidney biopsy may be considered if the diagnosis remains questionable (Figure 2).

When should a kidney biopsy be performed in pregnancy?

A kidney biopsy is generally considered in pregnancy when progressive kidney function impairment and/or severe proteinuria could interfere with pregnancy outcomes, and when establishing a diagnosis is needed to determine treatment (Table 1[50,58–63] and Figure 2).

Although an increased bleeding risk is reported in older series, recent data suggest that the procedure may be safe in experienced hands.[59,60] Furthermore, pregnancy is a valuable occasion to diagnose GD using kidney biopsy, in

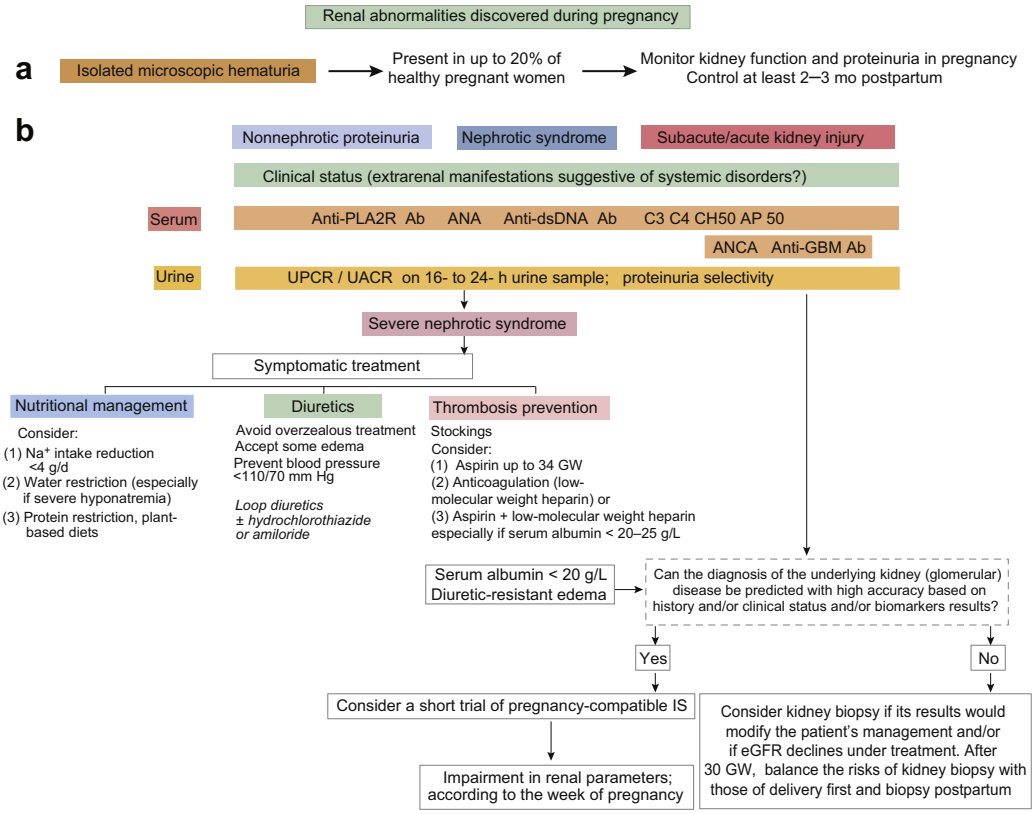

Figure 2 | Management of patients with renal abnormalities suggestive of a glomerular disease discovered during pregnancy. Ab, antibody; ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasm antibody; AP 50, alternative pathway activity 50%; CH50, complement hemolytic activity 50%; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate; GBM, glomerular basement membrane; GW, gestation weeks; IS, immunosuppressive treatment PLA2R, phospholipase A2 receptor; UACR, urinary albumin-to-creatinine ratio; UPCR, urinary protein-to-creatinine ratio.

several low- but also high-income countries.[11,64] However, in clinical practice, a kidney biopsy is rarely necessary in pregnancy, due to the rarity of the diagnosis of *de novo* disease or presumably GD, the availability of alternative diagnostic options, but also to late referral, because inducing delivery may be considered as a valuable alternative in late gestation, at least in highly resourced settings in which specialized perinatal care is widely available without charge.[65] For instance, the only series published in the last 5 years, from the largest referral center for complicated pregnancy in Mexico, encompasses only 20 kidney biopsies performed over a period of 5 years.[66]

MANAGEMENT OF SPECIFIC GDs IN PREGNANCY, INCLUDING KNOWN AND *DE NOVO* FORMS

This management refers to 2 distinct situations.

Table 1 | Considerations regarding the use of kidney biopsy in pregnant women

Kidney biopsy in pregnant women
(i) Clinicians are usually reluctant to perform a kidney biopsy during pregnancy. This is because of the increased risk of complications, estimated in a systematic review to be as high as 7%, compared with 1% after delivery (2% risk of major bleeding in the late second trimester[58]). The bleeding risk has been attributed to the increase in kidney blood flow and is thought to be reversible within ≈3 months after delivery.
(ii) More recent reports indicate that the risks of a kidney biopsy during pregnancy are minor when performed by an experienced physician and suggest that this procedure may be more frequently considered.[59,60]
(iii) The availability of laboratory tests, including the characterization of proteinuria, antibody workup for LN, ANCA, and anti-PLA2R antibodies, or the presence of highly selective proteinuria, may lead first to empiric treatment with postponement of biopsy to the postpartum period (Figure 1).
(iv) A normal ratio of soluble fms-like tyrosine kinase 1/placental growth factor may be useful in ruling out severe or superimposed preeclampsia.[50,61]
(v) Timing is crucial when considering kidney biopsy. In early pregnancy (<12 weeks), the risks of kidney biopsy are relatively low, and the advantages of precisely knowing the kidney disease are high. This profile of risks changes throughout pregnancy and may decrease after 30 to 34 weeks.
(vi) In some countries in which the health care system covers pregnancy but not later follow-up, the importance of establishing a clear diagnosis to guide subsequent therapy may outweigh the risks of kidney biopsy.
(vii) In kidney transplantation, the technically easier access to the grafted kidney may positively affect the risk-to-benefit ratio. In this context, the differential diagnosis includes graft rejection, recurrence, or a *de novo* glomerular disease and preeclampsia.[62,63]

ANCA, anti-neutrophil cytoplasm antibody; LN, lupus nephritis; PLA2R, phospholipase A2 receptor.

Table 2 | Obstetrical considerations regarding pregnancy in women with GDs

An obstetric perspective of GD in pregnancy
(i) The main obstetric risks are not specific to GD, as they include preeclampsia, preterm delivery, and intrauterine growth restriction.[67] The risk of intrauterine death is also increased, particularly in women with lupus nephritis, diabetic nephropathy, and other systemic immunologic diseases.[68]
(ii) The severity of preeclampsia is variable; although it may be particularly severe, requiring early therapeutic termination of pregnancy for maternal rescue at a nonviable gestation or fetal weight, preeclampsia superimposed on GD typically occurs late in pregnancy and is associated with relatively well-preserved fetal growth, thus being considered by some authors as the hallmark of "maternal" preeclampsia.[36,69]
(iii) Changes in proteinuria and blood pressure in patients with GD are not necessarily linked to preeclampsia, and may reveal flares of the underlying disease or, as for proteinuria, may be indicative of hyperfiltration stress. The differential diagnosis may be difficult (see dedicated section).
(iv) The risks for offspring are mainly linked to preterm delivery, which does not only occur in the context of preeclampsia. The reason for this increase is not clear. The risk of intrauterine growth restriction is also increased, particularly in women with hypertension. Further risks (namely, neonatal unit admissions and perinatal death) are essentially linked to preterm delivery and its consequences, and severe growth restriction.
(v) Ultrasound screening for fetal growth retardation should be performed monthly, as for other pregnancies at risk for fetal growth restriction. The frequency of using Doppler ultrasounds should be tailored on the basis of the presence and severity of abnormalities.
(vi) Obtaining available biomarkers to determine the angiogenic-antiangiogenic balance may assist in clinical management; however, their use in this context is not validated and, because of the heterogeneity of GD in pregnancy, strict surveillance by a skilled multidisciplinary team is the best way to prevent or attenuate severe complications in these high-risk pregnancies.
(vii) The use of low-dose aspirin prophylaxis is currently a standard of care in all pregnancies at risk for PE, including those in women with GD.[70] Early start (<12 gestational weeks) is indicated to warrant efficacy; treatment is stopped between 34 and 36 gestational weeks, or in the presence of risk conditions for imminent delivery.
(viii) Vitamin D deficiency should be corrected.[71,72]

GD, glomerular disease; PE, preeclampsia.

The diagnosis of GD is made before pregnancy

In this setting, prepregnancy multidisciplinary counseling and pregnancy planning are highly recommended. Multidisciplinary counseling should provide individualized information from both the nephrological and the obstetric perspectives (Tables 2[36,67–72] and 3 and Figure 3) about pregnancy-related risks for the mother (relapse/worsening of her GD and CKD, need for dialysis, and risk of hypertensive disorders of pregnancy) and for the offspring (Supplemental Table S3). Pregnancy planning allows for treatment optimization, notably discontinuation of drugs that are contraindicated in pregnancy.

The diagnosis of GD occurs during pregnancy

Management should consider the uncertainties surrounding the diagnosis if the latter is not supported by a kidney biopsy (Figure 4). General aspects of the management of severe proteinuria–nephrotic syndrome during pregnancy are shown in Figure 2.

Minimal change disease and FSGS. Data from case series (published since 2000) and case reports regarding pregnancy in patients with minimal change disease (MCD) and FSGS are summarized in Supplemental Tables S6 and S7.

Pregnancy in a patient with a history of MCD or of FSGS. In nonpregnant patients, the risk of relapse decreases with duration of remission, and is low after 6 years of relapse-free follow-up.[73,74]

Although data are limited, relapse of MCD during pregnancy has been reported in some old series[75] and in recent case reports.[76] The risk of relapse is likely higher in patients with corticosteroid-dependent MCD who are on maintenance immunosuppressive therapy (as in nonpregnancy patients). According to limited evidence, relapses are usually controlled by corticosteroids, and pregnancy outcomes are generally favorable. The best schedule of corticosteroid treatment for MCD/FSGS has not been fully established and should probably be determined on a case-by-case basis. Both bolus steroids[77] (methylprednisolone, 0.5–1 g intravenously, usually 3 administrations) and oral steroids (0.5–1 mg/kg per day) have been used.[76] A regimen of boluses followed by intermediate daily (or alternate days) oral doses may be considered, especially in women with risk factors (overweight, preexisting or gestational diabetes, or hypertension).

Calcineurin inhibitors are an alternative, but they require frequent monitoring of blood drug levels and screening for gestational diabetes.

In more recent reports of selected cases of MCD with high recurrence rates,[78,79] pregnancy outcome was favorable with maintenance rituximab therapy.

Table 3 | Practical recommendations for the counseling of women with GD who plan or start a pregnancy

(i) Take into account the woman's wish during the counseling, in a shared decision approach.
(ii) Integrate psychological aspects of pregnancy in women with GD, which are at least as important as medical aspects.
(iii) Individualize the assessment of pregnancy risks to the patient's clinical and biological features.
(iv) Give as much as possible an objective assessment of the risk of adverse pregnancy outcomes and progression of CKD. Highlight the areas of uncertainty, the individual response, as well as the lack of available precise data stratified per kidney function, degree of proteinuria and hypertension, and type of GD.
(v) In women with eGFR <30 ml/min at the start of pregnancy, discuss the issue of potential dialysis need, during pregnancy or shortly after delivery.
(vi) Explain the need to adapt treatment before/at the start of pregnancy and the therapeutic options in case of potential relapse/exacerbation of GD during pregnancy.
(vii) Discuss the potential need for induced/premature delivery and prematurity-related complications for the newborn.

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GD, glomerular disease.

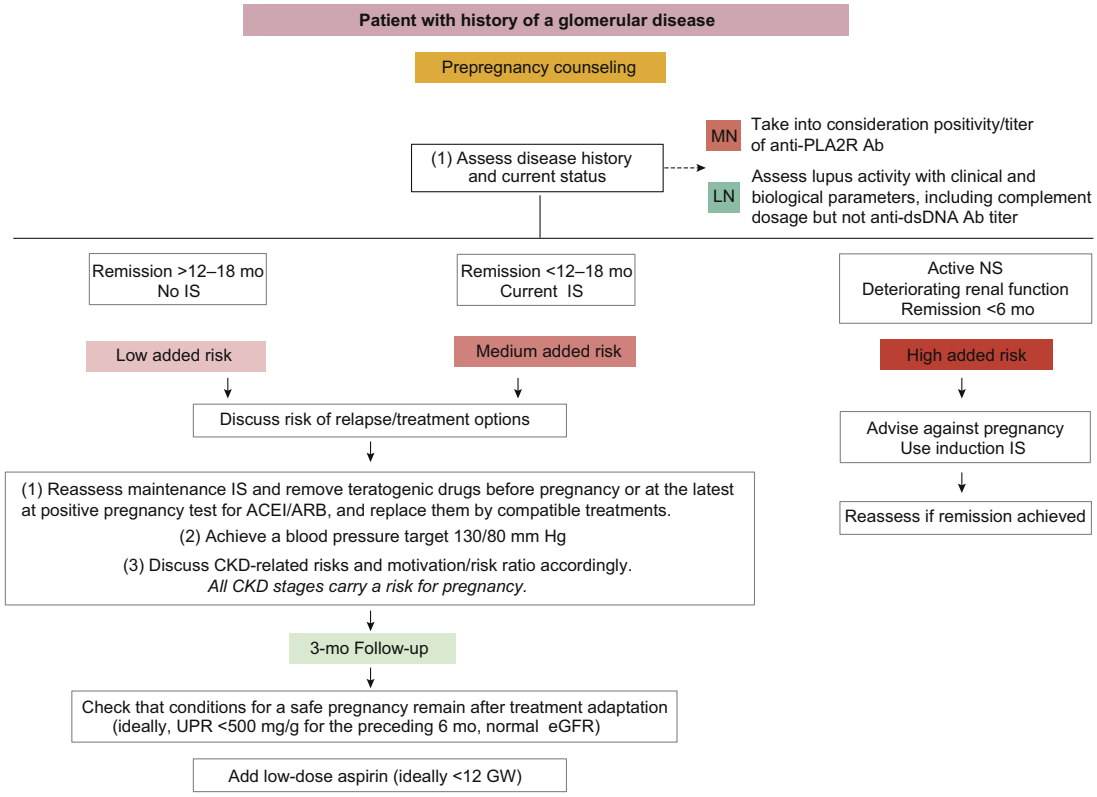

Figure 3 | Prepregnancy counseling and assessment of a woman with a glomerular disease. Ab, antibody; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate; GW, gestation weeks; IS, immunosuppressive treatment; LN, lupus nephritis; MN, membranous nephropathy; NS, nephrotic syndrome; PLA2R, phospholipase A2 receptor; UPR, urinary protein/creatinine ratio.

The spectrum of FSGS is broad, and the risks of adverse pregnancy outcomes are presumably moderate in the presence of mild proteinuria, whereas pregnancies with corticosteroid-resistant FSGS with persistent heavy proteinuria/nephrotic syndrome and/or CKD are at higher risk for maternal and fetal complications. In the absence of a large series, and with the heterogeneity of the disease, a case-by-case strategy is suggested.

The placental transmission of an unknown glomerular permeability factor from the mother with MCD or FSGS to the newborn, leading to transitory nephrotic syndrome, has been reported,[80–82] but breastfeeding is not contraindicated.

MCD or FSGS diagnosed in pregnancy. The occurrence of *de novo* MCD or FSGS during pregnancy is a rare event.[83–85] Its actual incidence has not been established. The diagnosis of MCD/FSGS is often presumed in the absence of kidney biopsy, mainly based on the selectivity of proteinuria, its abrupt onset, and, in the most favorable cases, a prompt response to corticosteroids (Box 1, case 1[84]). Therapeutic options are similar to those used for recurrences during pregnancy. Rituximab may represent a rescue therapy in patients with corticosteroid- and calcineurin inhibitor–resistant MCD/FSGS.

The diagnosis of FSGS in pregnancy may be challenging, as FSGS lesions are among the most common lesions found in kidney biopsies of women with a history of preeclampsia.[86–90] Collapsing lesions are probably much less frequent. Interestingly, in some reports, FSGS diagnosed in pregnancy may respond well to treatment, even in the presence of severe, collapsing lesions, and these observations plead for a proactive attitude toward treatment of FSGS in pregnancy.[91]

Membranous nephropathy (MN). Data from series (published since 2000) and case reports regarding pregnancy in patients with MN are summarized in Supplemental Tables S8 and S9.

The identification of several pathogenic autoantibodies has radically transformed the diagnosis and management of MN, including during pregnancy.[92,93] Most recently reported patients with MN in pregnancy have anti–phospholipase A2 receptor (PLA2R) antibodies.[94–96] Other autoantibody specificities are rare in this setting, with a single reported case with anti-thrombospondin type-1 domain-containing 7A antibodies.[97] Lupus-related MN is covered in another chapter.

Pregnancy in women with a history of MN. The existing literature on pregnancy in women with MN is extremely dated,[98,99] with the exception of a recent publication from Beijing, China.[95] Two series that included pregnancies occurring in the 1970s and 1980s reported poor maternal and fetal outcomes (24%–35% fetal loss; prematurity rate of 30%–43%) mainly due to first-trimester spontaneous abortions, in patients

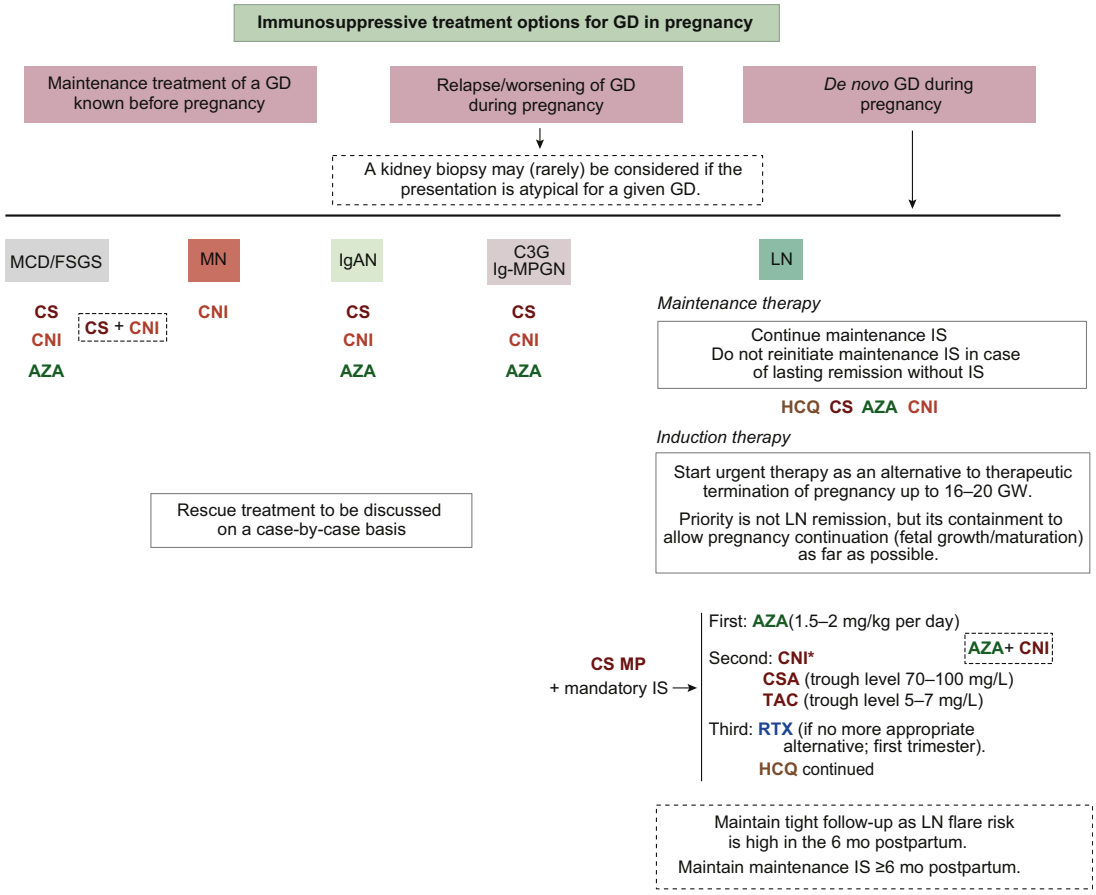

Figure 4 | Management during pregnancy of patients with a known relapsing or *de novo* glomerular disease (GD). AZA, azathioprine; C3G, C3 glomerulopathy; CNI, calcineurin inhibitor; CS, corticosteroids; CSA, cyclosporin A; FSGS, focal segmental glomerular sclerosis; GW, gestation weeks; HCQ, hydroxychloroquine; IgAN, IgA nephropathy; Ig-MPGN, Ig-associated membranoproliferative glomerulonephritis; IS, immunosuppressive treatment; LN, lupus nephritis; MCD, minimal change disease; MN, membranous nephropathy; MP, methylprednisolone; RTX, rituximab; TAC, tacrolimus.

who were hypertensive or nephrotic (or both) at conception or early in gestation.[100,101] Kidney function deteriorated in a single patient whose creatinine clearance was <48 ml/min at conception.

In the most recent Chinese series of 27 pregnancies in 25 women,[95] 10 adverse maternal-fetal events occurred, including fetal loss (11%), preterm delivery (26%), and severe pre-eclampsia (15%). Heavy proteinuria, especially before the 20th week of gestation, severe hypoalbuminemia, presence of anti-PLA2R antibodies, and absence of remission during pregnancy were risk factors for adverse maternal-fetal outcomes.

If the patient is proteinuric with an immunologically active disease (presence of high-titer anti-PLA2R antibodies), remission should be achieved with immunosuppressive treatment. If an anti-CD20 antibody is used, the manufacturer's recommendation is that conception should be avoided for 6 to 12 months after the last infusion, although the data reporting fetal toxicity are weak and sparse (see dedicated section).

In the event of an unplanned pregnancy in the setting of nephrotic syndrome, if, after being provided with extensive information, the patient still wishes to continue her pregnancy, strict monitoring should be offered. Calcineurin inhibitors are recommended as first-line therapy for their immunosuppressive effects and rather rapid anti-proteinuric effect[102] in the context of pregnancy-related glomerular hyperfiltration. Cyclophosphamide and anti-CD20 antibodies,[102,103] which are characterized by a delayed clinical response observed outside pregnancy, represent a rescue treatment in patients who do not respond to calcineurin inhibitors.

Monitoring should include repeated assessment of anti-PLA2R antibodies in the mother.[94] In the absence of specific guidelines, we recommend adjusting treatment according to the clinical situation, while taking into account the level of autoantibodies.

MN diagnosed during pregnancy. Few cases of *de novo* PLA2R-associated MN diagnosed during pregnancy have been published,[94,96] and diagnosis is usually based on the positivity of autoantibodies. However, if a kidney biopsy is performed, immunostaining of the paraffin-embedded biopsy with different specific antibodies may allow identification of the causal antigen. Regardless of the results of serology, recommendations for treatment are driven by the severity of the

Box 1 | Case 1

A 20-year-old woman was referred at 24 WG of her first pregnancy because of visual blurring and oliguria, and was found to have proteinuria (3.7 g/d), low serum albumin (23 g/L), and mild hypertension (140/95 mm Hg). She had gained 10 kg since the start of pregnancy, and leg edema was present. Urinalysis at the beginning of pregnancy was normal. Hematuria (20 RBCs per HPF) was found on urinalysis; proteinuria was mainly composed of albumin. The fetal biometry was at the 50th centile, and uteroplacental Doppler flows were normal. Proteinuria rapidly remitted, and BP normalized following betamethasone treatment to favor lung maturation.

Differential diagnosis

In favor of preeclampsia: Diagnostic criteria (proteinuria, edema, and hypertension) with onset after the 20th gestational week.

Suggesting a different diagnosis: Normal Doppler flows and fetal growth. BP and urine output normalization after steroid pulses. Selective proteinuria.

Not relevant for differential diagnosis: Microscopic hematuria (occasionally present in up to 20% of non-CKD pregnancies).

Indication for further tests

Kidney biopsy: Pro: gold standard for diagnosis. Cons: period of gestation; response to steroids.

Soluble fms-like tyrosine kinase 1/placental growth factor ratio: Pro: normal values make preeclampsia unlikely. Con: not formally validated in the differential diagnosis between CKD and preeclampsia.

Clinical development

Treatment with oral steroids was started (prednisone, 0.5 mg/kg per day) and slowly tapered, attaining complete remission. Spontaneous labor occurred at term, with delivery of a healthy female baby, adequate for gestational age.

Comments

This case is paradigmatic of the presentation of nephrotic syndrome, probably related to minimal change disease (rapid response to steroids and selective proteinuria) in pregnancy. Although a kidney biopsy is not formally contraindicated, the bleeding risks may be increased, and the prompt response to steroids concomitantly prescribed to improve fetal lung maturation was believed to be sufficient to guide treatment. No specific recommendation for steroid dosing in pregnancy is available (boluses or oral, initial dose). The use of serum biomarkers of preeclampsia may support the differential diagnosis but may be altered in forms of superimposed preeclampsia, even if this often occurs later in pregnancy. Normal fetal growth makes early preeclampsia unlikely. The frequency of controls is also not established (the available suggestions to perform a clinical control at least monthly may be hard to follow in low-resourced settings).

BP, blood pressure; CKD, chronic kidney disease; HPF, high-power field; RBC, red blood cell; WG, weeks of gestation.

Adapted from Montersino B, Menato G, Colla L, et al. A young woman with proteinuria and hypertension in pregnancy: is what looks and smells like preeclampsia always preeclampsia? *J Nephrol*. 2021;34:1677–1679.[84]

nephrotic syndrome. Treatment options in patients with MN and severe nephrotic syndrome are shown in Figures 2 and 4.

Transplacental transfer of PLA2R antibodies from the mother to the fetus has been reported. The concentration of autoantibodies, however, was much lower in cord blood, and the newborns were free of proteinuria at birth and at later visits. The transfer of PLA2R antibodies into breast milk has also been reported, with decreased levels of antibodies in the child when breastfeeding was discontinued.

In neonatal MN caused by anti–neutral endopeptidase antibodies, mothers do not develop a GD as they lack the neutral endopeptidase target antigen. MN in neonates is transient because maternal antibodies are short lived, but a few neonates develop severe MN with acute kidney injury that may require plasma exchange to decrease antibody titer.[104]

Primary Ig-associated membranoproliferative glomerulonephritis and C3 glomerulopathy in pregnancy.

C3 glomerulopathy and Ig-associated membranoproliferative glomerulonephritis known before pregnancy. Most of the studies describing the outcomes of pregnancy in patients with membranoproliferative glomerulonephritis (MPGN) were published before the distinction was made between C3 glomerulopathy (C3G) and Ig-associated MPGN (Ig-MPGN).[105–107] Pregnancy in women with MPGN in these dated studies carried a particularly high risk of severe outcomes: transient or irreversible worsening of kidney function in 10% to 30% and 2% to 10% of patients, respectively, fetal or perinatal loss in 10% to 30% of pregnancies, and prematurity or low weight for gestational age in 10% to 30% of newborns.[19,47,99,108–113] The grim prognosis reported in relatively old studies may simply reflect the severity of kidney disease and the high frequency of nephrotic syndrome.[19,99,113] No recent series have specifically addressed the outcomes of pregnancy in women with C3G and Ig-MPGN. There are no published data supporting the role of pregnancy in the exacerbation of complement activation and, thus, of the clinical and pathologic activity of C3G and Ig-MPGN.

Pregnancy, nonetheless, should be carefully planned in patients with C3G and Ig-MPGN, ideally with mild forms of these GDs or during a phase of clinical remission. For patients with clinical or laboratory worsening of the kidney disease during pregnancy (increased proteinuria, declining kidney function, or nephrotic syndrome), treatment options include oral corticosteroids, methylprednisolone pulses, azathioprine, and calcineurin inhibitors (Figure 4). A kidney biopsy should be considered on a case-by-case basis, particularly to assess the respective contributions of chronic/fibrotic lesions and acute/inflammatory changes in the decline of kidney function.[35] In patients with crescentic, rapidly progressing C3G and Ig-MPGN, eculizumab is an option.[114]

C3G and Ig-MPGN diagnosed during pregnancy. These types of GDs are rarely diagnosed during pregnancy, as the diagnoses are usually based on kidney biopsy findings (Figures 2–4). Treatment follows the indications mentioned above.

IgA nephropathy. Data from series reporting the outcome of pregnancy in patients with IgAN published since 2000 are summarized in Supplemental Table S10.

Box 2 | Case 2

A 35-year-old woman was referred at 14 WG of her second (unplanned) pregnancy, for nephrotic proteinuria and macroscopic hematuria with normal kidney function and mild hypertension. She denied alcohol and illicit drug use. Her first pregnancy had been uneventful. Her clinical history was remarkable for episodes of macroscopic hematuria, edema, and hypertension, starting 1 year earlier.

On admission, she was normotensive, with slight edema of the lower limbs. The initial proteinuria was 6.6 g/d, serum albumin was 22 g/L, and serum creatinine was 45 μmol/L. Urinary sediment was characterized by microhematuria. The baby's growth was normal. Lupus serology was negative. A kidney biopsy was performed at 18 WG and revealed IgA nephropathy (MEST score: M1E0S1T0C0), along with focal segmental sclerotic lesions ("tip" lesions).

Differential diagnosis

Preeclampsia: Despite the presence of classic features (proteinuria, edema, and hypertension), the onset was too early in pregnancy. The clinical history was suggestive of another kidney disease.

Glomerulonephritis: Normal Doppler flows and early onset suggested this diagnosis. History of macrohematuria in a young woman suggested IgA nephropathy. Although rare outside of pregnancy, nephrotic syndrome is probably more common in IgA nephropathy in pregnancy. Lupus nephropathy is the main differential diagnosis, together with membranoproliferative glomerulonephritis (albeit usually associated with renal function impairment and hypertension).

Indication for further tests

Kidney biopsy: Pro: gold standard for diagnosis. Con: higher risk of bleeding, especially after the 20^{t}h WG.

Soluble fms-like tyrosine kinase1/placental growth factor ratio: Usually indicated after 20 WG; the differential diagnosis ruling out preeclampsia is clear herein; the test could, however, be suggested monthly after 20 WG, to rule out superimposed preeclampsia.

Clinical development

Treatment with tacrolimus (3 mg/d) was started at 19 WG, and prednisone was continued for 8 weeks and tapered afterwards. At week 30, proteinuria had decreased to 0.56 g/24 h. At 35 WG, the patient experienced preterm rupture of membranes, and gave birth to a healthy female baby weighing 2484 g (35th centile) via cesarean delivery due to fetal bradycardia during labor.

At 6 months of follow-up after delivery, her proteinuria was stable at about 0.5 g/d, with normal kidney function and normal blood pressure.

Comments

This case underlines the fact that pregnancy may modify the natural course of kidney diseases, usually with an increase in proteinuria. The relatively high prevalence of IgA nephropathy in this age group should be considered in the differential diagnosis. A kidney biopsy, within the limits already mentioned, may be proposed particularly when, as in this case, the presentation is early in pregnancy (<20 weeks), and the differential diagnosis includes systemic diseases and potentially progressive glomerulonephritis, in which timely diagnosis and targeted treatment are crucial. The use of serum biomarkers of preeclampsia may help during follow-up, to rule out superimposed preeclampsia after 20 weeks.

MEST, M = mesangial hypercellularity, E = endocapillary proliferation, S = segmental glomerulosclerosis, T = dubular atrophy/interstitial fibrosis, C = crescents; WG, weeks of gestation.

Courtesy of Alejandra Orozco-Guillen.

IgAN diagnosed before pregnancy. IgAN is the most common primary GD worldwide, with a peak incidence between the second and third decades of life. This makes pregnancy a concern for many women with IgAN but has also allowed for the accumulation of a significant body of data regarding pregnancy outcomes in affected women[115] (Box 2, case 2).

In a recent register-based cohort study from Sweden, investigators compared outcomes from 327 pregnancies in 208 women with biopsy-verified IgAN and 1060 pregnancies in a matched reference population of women without IgAN, with secondary comparisons with sisters of women with IgAN.[116] IgAN was associated with an increased risk of preterm birth, preeclampsia, being born small for gestational age, and cesarean delivery. Absolute risks were low for intrauterine (0.6%) or neonatal (no cases) death and for a low 5-minute Apgar score (1.5%) and did not differ from the reference population. Sibling comparisons suggested increased risks of preterm birth, preeclampsia, and small for gestational age newborn in those with IgAN, but not of cesarean delivery. This study did not, however, include data on kidney biopsy, kidney function, or proteinuria, and therefore pregnancies could not be stratified on the basis of IgAN disease activity or severity.[116]

There have been 2 recently published systematic reviews and meta-analyses of kidney and pregnancy outcomes in IgAN—both of which included cohorts predominantly from Asia. The study by Wang *et al.* included 9 cohort or case-control studies, all with a control group of nonpregnant patients with IgAN, matched for age and kidney function.[40] Piccoli *et al.*, in contrast, included both case series and case reports, reporting on at least one pregnancy outcome, or long-term kidney function.[69] These cohorts included Asian and non-Asian patients with IgAN who have distinct presentation, severity of the disease, and treatment strategies. The different study design precludes any detailed comparisons, but most probably there is no difference in outcomes, once patients are stratified for baseline kidney function.

The results of these meta-analyses suggest that although pregnancy does not appear to confer a specific risk for kidney function impairment in IgAN with preserved kidney function, there is an increased risk of adverse pregnancy outcomes commensurate with the degree of prepregnancy kidney function impairment, blood pressure control, and proteinuria. The risks may be lower than those reported in other glomerular and systemic diseases.[117] However, there may be a more rapid loss of kidney function for those women who experience pregnancy-related complications.[118] IgAN may rarely be associated with "flares" during pregnancy, including episodes of visible hematuria, requiring a careful workup for other causes of hematuria. Some women may experience *de*

Box 3 | Case 3

A 36-year-old woman was referred at 12 WG of her second pregnancy. She had a history of lupus nephropathy (class III in a kidney biopsy performed 10 years earlier), previous lupus anticoagulant positivity (currently negative), chronic hypertension for 5 years, and normal kidney function. At referral, her treatment included prednisone, 10 mg; azathioprine, 100 mg; acetylsalicylate, 100 mg; and transdermal clonidine. She had developed gestational diabetes requiring insulin treatment.

During pregnancy, her kidney function remained normal. Antinuclear antibodies were stable at 1:320. Lupus anticoagulant was persistently negative, and anti-DNA antibodies, which were initially absent, fluctuated between 20 and 60 IU (last control before delivery: 29 IU; normal: <10 IU), with normal complement level. Proteinuria, which was initially about 0.5 g/24 h, slowly and progressively increased to 1.2 g/24 h before delivery.

At 36 WG, she was admitted to hospital for joint pain. Complement was normal, and lupus anticoagulant was negative.

At 37 WG, obstetric evaluation showed regular fetal growth (on the 10th centile) and normal Doppler flows. The patient had gained 2 kg after betamethasone was administered to improve lung maturation. A cesarean section was scheduled for the following day. During the night, sudden fetal bradycardia was detected on monitoring, and an emergency cesarean delivery was performed, delivering a dead-born female baby, weighing 2250 g (6th centile).

No sign of placental abruption was found. Immunohistochemistry performed on the fetal cardiac conduction system ruled out an inflammatory reaction. The placenta showed extensive fields of villitis and chronic intervillitis with widespread deposits of intervillous fibrin, and presence of thrombotic occlusion in a fetal vessel in the subchorionic area. The conclusion of the pathologist was placental malperfusion compatible with alterations on an autoimmune basis.

Intrauterine death and lupus

This case is a reminder of one of the rare, but terrible, challenges typical of lupus in pregnancy (i.e., death of the baby in a late stage of pregnancy). Although this devastating complication is usually associated with biological signs of lupus activity, the risk is increased also in their absence, as in this case, in which the only suggestive sign of a lupus flare was the appearance of moderate articular numbness and pain.

The patient had no classic clinical sign of placental dysfunction even if the baby was relatively small for gestational age (6th centile); most important, Doppler flows were normal. However, the availability of biomarkers defining the angiogenic-antiangiogenic balance, not available in the clinical context at the time this case was managed, would have been precious both as risk markers and for supporting a precise diagnosis.

Comments

Although, especially in small babies, the indications to follow pregnancy up to "full term" are sound, the late pregnancy-related risks may suggest delivering as soon as the "term" is reached. In this case, the choice to postpone delivery by 1 day (at 37 WG) was motivated by strategic issues (the following day being a Monday, with the full team available in the case of complications), in the presence of reassuring biological data and fetal ultrasounds.

This case is paradigmatic of one of the main challenges in following up patients with lupus in pregnancy: defining the timing of delivery. The study of angiogenic-antiangiogenic markers, presently widely available, may be useful also in the prediction of intrauterine death.[121,122]

WG, weeks of gestation.
Courtesy of Rossella Attini.

novo nephrotic syndrome or rapidly progressive glomerulonephritis, requiring more intensive treatment (see below).[19,119] Treatment options for IgAN in pregnancy are shown in Figures 2 and 4.

IgAN diagnosed during pregnancy. As IgAN can only be diagnosed through a kidney biopsy, it is unusual to make a new diagnosis during pregnancy, and the diagnosis is more commonly made postpartum. Clinical presentation with severe proteinuria during pregnancy is possible, and this possibility should be considered in the differential diagnosis of nephrotic syndrome.[19] Rapidly progressive glomerulonephritis due to IgAN has been described[120] but is rare, and it should be managed in the same way as vasculitis in pregnancy.

Lupus nephritis. The available data published after 2000 regarding pregnancy in patients with LN are summarized in Supplemental Table S11.

Pregnancy may be considered as a stress test for patients with LN, not only due to the presence and severity of CKD or of antiphospholipid syndrome (or autoantibodies), but also because pregnancy may trigger a lupus flare. Pregnancy in patients with LN remains a high-risk pregnancy (Box 3, case 3[121,122]).

LN diagnosed before pregnancy. The main risk for the mother is an LN flare. The risk of flares and of adverse pregnancy outcomes is higher in women with active lupus and decreases in parallel with the duration of remission before pregnancy.[123] A large meta-analysis performed in 2010, gathering data from 2751 pregnancies, quantified the risks of maternal and fetal complications: lupus flare (26%), hypertension (16%), nephritis (16%), preeclampsia (8%), and eclampsia (0.8%) in the mother; and spontaneous abortion (16%), stillbirth (3.6%), neonatal death (2.5%), and intrauterine growth restriction (13%) in the fetus. The successful pregnancy rate was 77%, and the preterm birth rate was 39%.[68] Complications and poor pregnancy outcomes, in this analysis and others, were associated with active lupus and particularly LN.[124] Presence of lupus anticoagulant and kidney damage modulate the risk of adverse pregnancy outcomes.[123,125]

Pregnancy outcomes, conversely, are better in patients with controlled lupus and LN in remission,[123,126] with no significant renal damage.[125] The risk of kidney flare occurring during pregnancy is higher in women with persistent lupus activity at the time of conception, and is lower when LN remission has been present for at least 12 months before conception.[127] Figures 3 and 4 summarize the general principles for the management of pregnancies in women with systemic lupus or history of LN.[128–131]

Table 4 | General considerations regarding the management of hypertension in pregnant women with GD

How should BP be monitored and hypertension diagnosed in pregnancy?
(i) Monitoring blood pressure in pregnant patients with GD is mandatory because in women with even mild CKD the risk of hypertensive disorders during pregnancy is increased.[8,156] Fetal survival is decreased when BP is >140/90 mm Hg during the preconception period.[37,110]
(ii) To avoid overdiagnosis (white coat hypertension), which almost reaches 30% in the third trimester, or underdiagnosis (masked hypertension, defined as normal BP measurements in a physician's office but elevated during the day-to-day activities), out-of-office BP measurement, when available, is preferred.[156]
(iii) The prevalence of resistant hypertension (i.e., hypertension not fully controlled by treatment) is elevated (up to 24%) in the second half of high-risk pregnancies, including in women with GD.[157]
(iv) Cutoffs for the diagnosis of hypertension in pregnancy are an office systolic BP ≥140 mm Hg and/or office diastolic BP ≥90 mm Hg, on at least 2 occasions measured 4 hours apart.[158]
What is the BP target in pregnant women with GD?
(i) No guidelines are specifically targeted at BP control in pregnant women with CKD or GD.
(ii) A recent position statement on CKD in pregnancy, from the Italian Society of Nephrology, suggests personalizing BP targets, with the aim to attain at least the targets recommended outside of pregnancy.[43] Recent clinical practice guidelines from the United Kingdom,[159] again not specifically addressing GD, but more broadly CKD, recommend a target BP of ≤135/85 mm Hg during pregnancy.
(iii) We recommend a target BP of 130/80 mm Hg, unless systolic BP is consistently <110 mm Hg or diastolic BP is consistently <70 mm Hg, and/or symptomatic hypotension occurs. The recommendation may also be supported by a recent study reporting improved outcomes when maintaining patients on BP medication or initiating treatment early in pregnancy for chronic hypertensive pregnant women with a systolic BP of ≥140 mm Hg or a diastolic blood pressure of ≥90 mm Hg, or both.[160]
When should ACEi/ARBs be discontinued in patients with GD planning a pregnancy?
(i) This question is still debated.
(ii) In the presence of CKD and GD characterized by significant residual proteinuria, some experts prefer modifying treatment only when pregnancy is confirmed. This avoids prolonged cessation of ACEi/ARB agents while waiting to conceive, which may take months or even years, especially if past immunosuppression has had an impact on fertility.
(iii) Other experts prefer to stop ACEi/ARB agents before pregnancy and consider that the magnitude of proteinuria increase will modify patient counseling.
(iv) The fetal risks may be higher with early exposure to ARB agents,[161] but the effects of hypertension, the underlying diseases, and the effects of specific treatments may be difficult to distinguish.[162–164] The advantages of prolonging renoprotective treatment and of starting pregnancy with low-grade proteinuria, versus the risk of adverse fetal outcomes, should be weighed on a case-by-case basis, taking into consideration kidney function, severity of proteinuria, type of GD, BP control, and patient adherence to treatment and preferences.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; GD, glomerular disease.
The choice of antihypertensive medications may vary from one country to another.

The benefit over risk ratio of hydroxychloroquine use is favorable,[42,126,132] and this drug is recommended in pregnancy. Steroids, azathioprine, and calcineurin inhibitors may be used during pregnancy as well.[129,133,134] Rituximab may be considered in the absence of more appropriate alternatives in severe and resistant cases. Belimumab, voclosporin, and anifrolumab are not recommended during pregnancy because of lack of experience.

Low-dose aspirin is strongly recommended in all patients with LN. In the presence of antiphospholipid syndrome, aspirin should be added to heparin[129] whenever possible during the preconception period to prevent fetal loss, placental insufficiency, and thrombotic complications.

Furthermore, in the presence of anti-Ro/SSA antibodies, systematic fetal heart rhythm monitoring is usually advised for early detection of fetal atrioventricular block (detected in 1%–2% of anti-Ro/SSA pregnancies).[135–137] Routine screening, however, has recently been challenged and may be reserved for patients with a history of congenital heart block.[137]

LN diagnosed during pregnancy. LN may be diagnosed during pregnancy based on clinical status (extrarenal manifestations suggestive of lupus), positivity of autoantibodies (mainly anti–double-stranded DNA and anti-Smith antibodies), features of complement activation (low serum C4, C3, and complement total activity 50% [CH50] levels) and, more rarely, with a kidney biopsy. Proliferative LN in pregnancy with declining renal function requires urgent therapy and the discussion of therapeutic termination of pregnancy in case of organ-threatening disease. The aim of treatment is, at least, to attempt to contain LN so as to allow pregnancy continuation and fetal growth for as long as possible. Treatment options are shown in Figure 4.

Vasculitis in pregnancy. Vasculitis typically occurs at an older age, but women of childbearing age are not spared.[138–142] Data on pregnancy outcome are related to the 2 main forms of kidney vasculitis, anti-neutrophil cytoplasm antibody vasculitis (AAV) and IgA vasculitis.

Vasculitis diagnosed before pregnancy. The risk of relapse during pregnancy in women with AAV remains difficult to predict, and the clinical spectrum ranges from mild flares in most cases (crusting rhinitis, skin lesions, and arthritis) to severe complications mostly documented in case reports (alveolar haemorrhage, crescentic glomerulonephritis, or thrombotic microangiopathy).[143–145] A report of 15 pregnancies in 13 women (11 granulomatosis with polyangiitis and 2 microscopic polyangiitis) with prior diagnoses of AAV, all in remission for >6 months at conception, showed favorable outcomes. In all planned pregnancies, women were switched to azathioprine in combination with

Table 5 | Antihypertensive drugs for emergency and nonemergency hypertensive disorders of pregnancy in women with GD

Setting	Drug	Route	Dose	Contraindications	Adverse effects
Emergency	Labetalol	I.v.	10–20 mg initially, then 20–80 mg every 10–30 min to a maximum cumulative dose of 300 mg; infusion: 1–2 mg/min	Second- or third-degree AVB Systolic heart failure Asthma bradycardia	Bronchoconstriction Fetal bradycardia
	Urapidil	I.v.	12.5–25 mg as bolus injection; 5–40 mg/h as continuous infusion		Hypotension Reflex tachycardia
	Hydralazine	I.v.	5 mg, then 5–10 mg every 20–40 min		Hypotension Reflex tachycardia Headaches
No emergency	Labetalol	Oral	100 mg bid to 800 mg tid	Second- or third-degree AVB Systolic heart failure Asthma Bradycardia	Bronchoconstriction Fetal bradycardia
	Nifedipine	Oral	20–30 mg bid		Reflex tachycardia Headaches
	α-Methyldopa	Oral	250 mg bid to 1000 mg tid; titrate every 48 h		Orthostatic hypotension Sedation

AVB, atrioventricular block; bid, 2 times a day; GD, glomerular disease; tid, 3 times a day.

prednisolone or additional cyclosporine. Two patients experienced a relapse: one developed crescentic glomerulonephritis that was successfully treated by plasma exchange and i.v. Ig, and one presented with mild crusting rhinitis and subglottic stenosis.[138] Transplacental transfer of anti-myeloperoxidase–anti-neutrophil cytoplasm antibody with neonatal alveolar hemorrhage has been described in a newborn.[146] IgA vasculitis flares during pregnancy have occasionally been reported, and are mostly mild, with purpura and arthralgias; overall, kidney outcomes have been reported as good.[147,148] In the largest case series of 247 pregnancies in women with IgA vasculitis in pregnancy,[149] no flares were observed, but 43 unsuccessful pregnancies (17.4%) were recorded, with 17 preterm deliveries (8.3%).

Women with IgA vasculitis furthermore had an ≈2-fold risk of spontaneous abortion and preterm delivery and a high risk of gestational hypertension (odds ratio, 4.7).[141]

Vasculitis diagnosed during pregnancy. One systematic review[150] identified 27 cases of *de novo* AAV in pregnancy, most of which occurred in the second trimester. Most women were treated with steroids (89%), but 37% received cyclophosphamide (mainly before 2005), and a minority received azathioprine, i.v. Ig, plasma exchange, or no therapy. Serious complications included preeclampsia (29%) and maternal death (7%). Most infants were born alive and

Table 6 | In addition to the general indications for dietary management in pregnancy, for pregnancies in patients with GDs, the following indications may be considered

Avoidance of nutritional deficits
(i) Folic acid: water soluble, indicated in the prepregnancy phase for the prevention of neural tube disorders; may be lost in the urine in nephrotic patients. (ii) Vitamin D: frequently reduced in advanced CKD; low levels are associated with higher risk of preeclampsia. (iii) Vitamin B12: may be reduced, particularly in patients on plant-based and low-protein diets. (iv) Iron may be reduced, especially in patients on plant-based and low-protein diets or lost in nephrotic syndrome.[172,173] Although dosing is not advised in the general population, it is advised in patients with CKD with GD, at least by some experts.[43]
Avoidance of excessive weight gain
Excessive weight gain is associated with adverse pregnancy outcomes, particularly preeclampsia and hypertensive disorders of pregnancy.[174,175] The simple rule of avoiding a weight gain of >1 kg per month should be adapted to prepregnancy body mass index. Use of corticosteroids, when needed, should be balanced against this risk.
Avoidance of high-protein diets
Particularly in CKD stages 3–5 and in the presence of significant proteinuria, plant-based diets are safe in pregnancy; results from noncontrolled series suggest that protein-restricted diets and plant-based diets may contribute to proteinuria stabilization in pregnant women with GD.[176–178] The safety of such dietary measures in pregnancy is validated, provided that nutritional deficits are controlled and supplemented when needed.[179,180]
Food quality
Compelling, albeit limited, data suggest that controlling quality of food and the avoidance of additive and preservation products may play a role in the stabilization of kidney function in pregnancy.[181]

CKD, chronic kidney disease; GD, glomerular disease.

in the third trimester. Pregnancy termination occurred in 23%, but only one intrauterine death was reported, shortly after initiation of therapy; congenital abnormalities were rare. The authors concluded that *de novo* AAV in pregnancy can result in uncomplicated pregnancies; however, serious maternal risks exist.[150] A second review[151] included 110 patients with AAV, in whom a vasculitis diagnosis was made before pregnancy in 69, during pregnancy in 32, and after pregnancy in 9. There were 28 preterm pregnancies, 15 abortions, and 3 stillbirths. Three maternal deaths due to a vasculitis flare were reported. The authors do not report significant differences between those who were diagnosed before and during pregnancy.[151]

Postinfectious glomerulonephritis, unusual and complex situations. Virtually all GDs have been reported, at least occasionally, in pregnancy—with reporting biases (preferential report of extreme cases, and cases with a good outcome). The immunologic state and glomerular hyperfiltration characteristic of pregnancy may modulate the clinical, biological, and pathologic picture. Among the rare forms of GDs diagnosed in pregnancy, acute, postinfectious glomerulonephritis has occasionally been reported,[152–155] with some cases characterized by intense proteinuria, even in the absence of superimposed preeclampsia.

GENERAL MANAGEMENT OF GD IN PREGNANCY

General considerations regarding hypertension and its treatment in pregnant women with GDs are summarized in Tables 4[8,37,43,110,156–168] and 5.

A detailed discussion on the use of immunosuppressive drugs in pregnant patients is beyond the scope of this review, and the reader may refer to recently published extensive reviews for details.[169–171] Supplemental Table S12 summarizes the main basic information regarding the most commonly employed drugs in pregnancy. Supplemental Table S13 summarizes the main considerations regarding breastfeeding in women with GDs.

Recommendations for the dietary management of pregnant patients with GD are summarized in Table 6.[43,172–181]

Special considerations from middle- to low-income countries on pregnancy in patients with GDs

Although GDs in pregnancy raise the same clinical challenges worldwide, some logistical aspects may modulate their management during and after pregnancy in highly resourced versus middle-/low-resourced[182,183] countries.

The incidence of GDs, as well as of CKD from all causes, is higher in many middle- to low-income countries. The chances that a young woman would be diagnosed with a GD, or another form of CKD, in pregnancy is therefore higher.[11,184,185]

In some countries, such as Mexico, maternal care is available free of charge for all citizens, but the coverage is extended only for a short period after delivery. This has supported the policy of performing a kidney biopsy during pregnancy or immediately thereafter not to lose a unique opportunity for timely diagnosis and treatment.[184] Likewise, neonatal intensive care units are scarcely available in several middle- to low-income countries; hence, clinical management favors fetal maturation whenever possible to 34 weeks, with the aim to avoid the need for admission to neonatal intensive care units. Such strategy obviously carries an increase in maternal risks and may lead to a more aggressive attitude toward pregnancy termination in high-risk pregnancies.

CONCLUSIONS

Pregnancy in women with GDs remains challenging for nephrologists and obstetricians worldwide. The advances in obstetric care have not only improved prognosis but have led to a more open attitude toward pregnancy in women with GDs, whereas the acknowledgement of the impact of even minor kidney involvement on pregnancy outcomes may guide timely interventions.

The involvement of patients in shared choices is the key for facing, in the best possible way, the challenges of a high-risk pregnancy. Although preconception information and preparation is advisable, discovery of a kidney disease in pregnancy is not rare and may raise important ethical and psychological issues.

Collaborative prospective studies are still needed to refine our knowledge of pregnancy outcomes in these patients with relatively rare kidney diseases.

DISCLOSURE

All the authors declared no competing interests.

AUTHOR CONTRIBUTIONS

The multidisciplinary international working group is composed of experts in the field of glomerular diseases (GDs) and/or of pregnancy in women with kidney diseases. FF and GBP coordinated the group. NS and GC reviewed published series and cases reports related to pregnancy in women with GDs. GA and GR reviewed and amended the whole manuscript. The sections on IgAN; MCD and FSGS; MN; LN; MPGN and C3G; postinfectious glomerulonephritis, unusual and complex situations; and vasculitis were drafted by JB; JW and VA; PR; ED, NC-C, and LL; MP and FF; AOG; and EZ and AKar; respectively. The sections on hypertension, dietary management, kidney biopsy, and immunosuppressive drugs were drafted by GW; GBP, FL, and RA; AOG and GBP; and GM, CP, and AKat; respectively. The sections on renal function in pregnancy, epidemiology of GD in pregnancy, complement assays, and antiangiogenic biomarkers were drafted by KW, SJ, VG and EL, and MN, respectively. The section on obstetric perspective was drafted by HL, DD, and VT. The section on special considerations from middle- to low-income countries was drafted by CL, JP, and VS-A. FF drafted the figures, and GBP drafted the cases. FF and GBP drafted the manuscript, incorporating all the sections. All the authors reviewed the draft and subsequently the amended version of the manuscript with significant input.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Table S1. Interpretation of kidney function tests in pregnant patients with glomerular disease (GD). CKD, chronic kidney disease; UACR,

urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio; WG, weeks of gestation.

Table S2. Lower limit of normal of serum albumin and upper limit of normal of serum creatinine, according to gestational age. Based on data from Larsson *et al.*[S1] © 2008 The Authors Journal compilation © RCOG 2008 BJOG An International Journal of Obstetrics and Gynaecology.

Table S3. Adverse pregnancy outcomes in patients with chronic kidney disease and in their offspring.

Table S4. Published data regarding the impact of pregnancy on complement assays and tests.

Table S5. Summary of the impact of pregnancy and its complications on the complement system.

Table S6. Summary of series reporting the outcome of pregnancy in patients with focal segmental glomerular sclerosis (FSGS), published since 2000.

Table S7. Summary of case reports of pregnancy in women with focal segmental glomerular sclerosis (FSGS) or minimal change disease (MCD).

Table S8. Summary of series reporting the outcome of pregnancy in patients with membranous nephropathy (MN), published since 2000.

Table S9. Summary of case reports of pregnancy in women with membranous nephropathy (MN).

Table S10. Summary of series reporting the outcome of pregnancy in patients with IgA nephropathy (IgAN), published since 2000.

Table S11. Summary of series reporting the outcome of pregnancy in patients with lupus nephritis (LN), published since 2000.

Table S12. Considerations regarding the use of distinct immunosuppressive drugs during pregnancy.

Table S13. Considerations regarding breastfeeding in women with glomerular disease (GD).

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