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REVIEW

Glomerular Disease in Women

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Gender differences exist in the prevalence of glomerular diseases. Data based on histological diagnosis underestimate the prevalence of preeclampsia, which is almost certainly the commonest glomerular disease in the world, and uniquely gender-specific. Glomerular disease affects fertility via disease activity, the therapeutic use of cyclophosphamide, and underlying chronic kidney disease. Techniques to preserve fertility during chemotherapy and risk minimization of artificial reproductive techniques are considered. The risks, benefits, and effectiveness of different contraceptive methods for women with glomerular disease are outlined. Glomerular disease increases the risk of adverse outcomes in pregnancy, including preeclampsia; yet, diagnosis of preeclampsia is complicated by the presence of hypertension and proteinuria that precede pregnancy. The role of renal biopsy in pregnancy is examined, in addition to the use of emerging angiogenic biomarkers. The safety of drugs prescribed for glomerular disease in relation to reproductive health is detailed. The impact of both gender and pregnancy on long-term prognosis is discussed.

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In a global survey of histological diagnoses of glomerular disease, including more than 40,000 biopsy results, 47% of diagnoses were made in women, compared with 53% in men.[1] Overall, female preponderance was evident in both lupus nephritis and thin basement membrane nephropathy, with a diagnosis of IgA nephropathy being more commonly made in men. Therefore, in regions where the incidence of lupus nephritis was high, glomerular disease diagnoses occurred more frequently in women than men. Gender differences in systemic lupus erythematosus (SLE) are greatest during reproductive age, with reported male:female ratios of 1:8 to 15, compared with ratios of 1:2 to 6 and 1:3 to 8 in prepubertal and postmenopausal cohorts, respectively.[2–4] The pathologic mechanisms that underlie this gender disparity remain elusive, although epigenetic and immunomodulatory effects of endogenous sex hormones are hypothesized.[4] Asian and Hispanic women, as well as women of African ancestry, have an additional risk of lupus nephritis conferred by their ethnicity and race.[5]

A weakness of using histological diagnoses as a measure of renal disease prevalence is that findings are confounded by differences in renal biopsy threshold. Where women have lower levels of proteinuria and blood pressure,[6] thresholds for biopsy may not be reached and histological disease prevalence may not reflect true population prevalence. Equally, glomerular conditions that have clinical, rather than histological, criteria for diagnosis will be omitted from any studies based solely on biopsy data. Preeclampsia affects 3% to 5% of pregnancies,[7] which means that it is estimated to be the commonest glomerular disease in the world. Pathognomonic renal changes include diffuse endothelial swelling and vacuolation of podocytes ("endotheliosis")[8]; however, preeclampsia is principally a clinical diagnosis made on the basis of *de novo* hypertension and proteinuria after 20 weeks' gestation, and renal biopsy is rarely required. Although proteinuria that is either detected before 20 weeks' gestation or persists postpartum warrants referral to nephrology services for the exclusion of coexisting renal disease[9]; preeclampsia is a glomerular disease that is predominantly diagnosed and managed by obstetricians,[10] rather than nephrologists. The importance of preeclampsia as a leading cause of glomerular pathology in women is therefore underestimated by both renal biopsy and nephrology referral data.

Depending on the health care setting, there may be more opportunities for the diagnosis of asymptomatic glomerular disease in women compared with men. Gender differences in the utilization of primary care

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during the reproductive and mid-life years are recognized, with higher rates of consultation by women than by men.[11] Reproductive health forms an important part of this difference and attendances for contraception, maternity, and postpartum care may include blood pressure monitoring and urinalysis. It is, however, important to recognize the potential pitfalls of such opportunistic screening for glomerular disease; namely, the assumption that proteinuria is not likely to be glomerular in origin in a young woman.

Fertility

There are limited data about the effects of glomerular disease on fertility. At the midpoint of the menstrual cycle, there is positive feedback between estrogen and the hypothalamic-pituitary axis, which leads to a surge in luteinizing hormone (LH) and ovulation. Following ovulation, the cells of the follicle form the corpus luteum, which secretes progesterone in preparation for implantation. If implantation does not occur, the corpus luteum regresses and menstruation occurs. In advanced chronic kidney disease (CKD), low levels of estrogen confer negative feedback. Although levels of LH are higher, there is no midcycle surge, and cycles become anovulatory.[12] Small cohort studies show that there is progression from a regular menstrual cycle to oligomenorrhea and amenorrhea as the severity of underlying CKD increases, although levels of renal dysfunction at which these changes become clinically significant, and the relative contribution from specific glomerular disease pathologies, remain unknown.[12] Contemporaneous European cohorts of women with CKD due to different etiologies show that pregnancy rates in transplant recipients and in patients requiring dialysis are approximately 10% and 1%, respectively, of those in the general population.[12,13] The degree to which this marked reduction in pregnancy in CKD is due to reduced fertility rates or is confounded by voluntary childlessness is unknown.

Of all glomerular pathologies, the effects of SLE on female fertility are best described. Data on the impact of other glomerulopathies on female fertility are insufficient to determine a disease-specific effect above that of CKD. A cohort study of women receiving fertility treatment led to an estimate that SLE contributes to 1% to 2% of infertility, which is higher than expected given an estimated disease prevalence of 1 in 2000 adult women.[14,15] In small cohorts of women with lupus, menstrual irregularity has been found to correlate with levels of disease activity.[16] Underlying pathologic mechanisms are hypothesized to be multifactorial,[15] including the effects of CKD on the menstrual cycle, autoimmunity as evidenced by the detection of anti–corpus luteum antibodies,[17] endometriosis driven by altered immune function,[18] and a reduced ovarian reserve associated with the therapeutic use of cyclophosphamide.

Cyclophosphamide is an alkylating agent that causes dose- and age-dependent gonadotoxicity, including premature ovarian failure.[19,20] Fertility preservation should be considered before the use of cyclophosphamide in all premenopausal women. Pretreatment preservation of oocytes and gametes can be undertaken, but this typically requires ovarian stimulation. Given that the female predominance of lupus is hypothesized to be due to the modulation of the immune system by sex hormones, there is a concern that artificial ovarian stimulation in lupus confers a risk of disease exacerbation and thrombosis, especially in the context of circulating antiphospholipid antibodies. Published data on the risks of ovarian stimulation are limited[21,22] and conflicting,[22] and there is an absence of prospective trials. Natural cycle oocyte retrieval negates the need for ovarian stimulation and has been described in a small cohort of 7 women with CKD, including 5 women with lupus nephritis.[23] However, this technique continues to be considered experimental, with insufficient outcome data. An alternative to preservation of reproductive tissue is the use of LH-releasing hormone analogs to inhibit ovarian function for the duration of cyclophosphamide treatment. These are hypothesized to preserve future fertility via a protective inhibition of the hypothalamic-pituitary axis or a reduction in ovarian blood supply and subsequent exposure to cyclophosphamide. A small trial of 20 women with lupus nephritis showed a reduction in premature ovarian failure with the use of LH-releasing hormone analogs.[24] Larger randomized controlled trials[25,26] and meta-analysis data[27] examining the use of LH-releasing hormone analogs during cyclophosphamide treatment for cancer demonstrate a safe and effective reduction in premature ovarian failure.

Over recent decades, the prognosis for many glomerular diseases has improved. With increasing numbers of women achieving disease quiescence,[21] and social trends of increasing maternal age,[28] the issue of reproductive technology has become increasingly relevant for women with glomerular disease. A recent retrospective study of 97 cycles of *in vitro* fertilization (IVF) in women with SLE and/or antiphospholipid syndrome showed that IVF was safe and conferred comparable pregnancy outcomes to the general population. Lupus flares and thrombotic events occurred in only 8% of cycles, and half of these were attributed to reduced concordance with treatment. However, it should be noted that only 4 women in the study had nephritis, maternal disease was quiescent or well controlled in all women, and none had residual renal

insufficiency.[29] In addition to lupus disease flare, a concern with IVF in women with underlying renal disease is the possibility of ovarian hyperstimulation, which is associated with the overproduction of vasoactive cytokines and inflammatory mediators leading to intravascular fluid loss, thromboembolism, and acute kidney injury. A Cochrane review including 73 randomized controlled trials demonstrated that IVF protocols that induce pituitary desensitization using gonadotrophin-releasing hormone antagonists reduce the incidence of ovarian hyperstimulation compared with the prolonged use of gonadotrophin-releasing hormone agonists.[30] This is mirrored in small cohorts of women with lupus and antiphospholipid syndrome.[29] For this reason, IVF protocols using gonadotrophin-releasing hormone antagonists should be considered for all women with glomerular disease, particularly lupus. In addition, single-embryo transfer should be advised for women with underlying glomerular disease due to the additive risks of adverse pregnancy outcome conferred by multifetal pregnancy at all stages of CKD.[31,32]

Contraception

Unplanned pregnancies occur throughout the spectrum of renal disease. There is a paucity of contemporary published data on contraception counseling and provision for women with glomerular disease. Older questionnaire data revealed that women with advanced CKD are vulnerable to unintended pregnancy, as they are sexually active in the absence of contraception, with only a minority of women discussing contraception with their nephrologist.[33] Even in transplant cohorts, in whom contraceptive counseling is necessary due to the need to avoid pregnancy within the first year, and in any women taking teratogenic medication, between one-third and one-half of pregnancies are unplanned.[34,35] A survey of 212 women with lupus revealed that 46% had a risk of unintended pregnancy, with 23% having unprotected sex "most of the time."[36] It is the experience of the authors that contraceptive advice is often inadequate, despite the increased risk of adverse pregnancy outcomes conferred by underlying CKD.

The ideal contraceptive is effective, safe, and acceptable to the patient and her partner. Effectiveness rates should judged by the "typical"-use failure rates, rather than presuming "perfect" use, as differences exist (Table 1).[37] For example, typical use of condoms results in approximately 1 in 5 women falling pregnant within a year of use, and they cannot therefore be recommended as an effective long-term method for preventing pregnancy. In contrast, long-acting reversible contraceptive methods, including the intrauterine device (IUD) and the subdermal implant, have "perfect"-use and "typical"-use failure rates that are lower than that of female sterilization.

Estrogen-containing contraceptives include the estrogen-containing (combined) pill, the vaginal ring, and the contraceptive patch. All estrogen-based methods confer an increased risk of hypertension, venous thromboembolism, arterial disease, and breast and cervical cancers. Whether this confers an unacceptable absolute risk depends on a woman's glomerular disease etiology, cardiovascular risk factors, and the burden of immunosuppressive therapy. Given that lupus is hypothesized to be due to the modulation of the immune system by sex hormones, there are concerns that estrogen-containing agents may cause disease exacerbation or flare, and estrogen-containing contraceptives are contraindicated in lupus. Although in a randomized controlled trial, women with stable

Table 1. Contraception in women with glomerular disease

Contraceptive method	Unintended pregnancy rate within 1st year of use (%)[37]		Contraindications in glomerular disease	Other considerations
	Perfect use	Typical use		
Estrogen-containing methods (pill, patch, ring)	0.3	9	• Lupus • VTE • Vascular disease	• Breast cancer risk • Cervical cancer risk with immunosuppression • VTE risk in nephrotic syndrome
Progesterone-only pill	0.3	9	• None	• Longest re-dosing interval with desogestrel (may improve typical use) • Possible breast cancer risk, especially >40 yr
Progesterone IUD (Mirena)	0.2	0.2	• None	• Possible breast cancer risk, especially >40 yr • Effective with immunosuppression, no evidence of increased infection.
Progesterone implant (Nexplanon)	0.05	0.05	• None	• Possible breast cancer risk, especially >40 yr
Copper IUD	0.6	0.8	• None	• No associated hormonal risk
Male condom	2	18	• Ineffective for long-term use	• Protects against HIV and STI
Female condom	5	21		
None	85	85		

IUD, intrauterine device; STI, sexually transmitted infection; VTE, venous thromboembolism.

disease who were lupus anticoagulant and anti-cardiolipin antibody negative and with no history of thromboses, there was no increased risk of flare in the those given the combined oral contraceptive (with 35 μg estradiol) compared with placebo.[38] That study, however, did not address women with proteinuria >0.5 g per 24 hours. The risk of thromboembolism means that any proteinuric glomerular disease is a relative contraindication for estrogen-containing methods, particularly now that more effective nonestrogen-containing methods exist.

Progesterone-based methods of contraception include the progesterone-only pill, the progesterone-containing IUD (Mirena, Bayer, Whippany, NJ) and the subdermal implant (Nexplanon, Merck & Co. Inc, Whitehouse Station, NJ). These methods do not have the same risk profile as estrogen-containing methods and are appropriate for women with glomerular disease and CKD.[9] The theoretical risk of IUD failure due to inhibition of the uterine inflammatory response by immunosuppressive therapy is not borne out, with no evidence of excess IUD failure following transplantation.[39–41] There is also no evidence of increased rates of IUD-associated pelvic infection in cohorts of immunosuppressed women.[40,42]

Studies of breast cancer risk in women using hormonal methods of contraception are inconsistent in their findings. A recent large prospective population study of 1.8 million women revealed a 20% increased relative risk of breast cancer in women using estrogen-containing or progesterone-only methods of contraception, but the absolute increase in risk was just 2 per 100,000 in women younger than 35 years.[43] This very low absolute risk must be weighed against benefits in preventing unplanned pregnancy, as well as reducing rates of ovarian, endometrial, and colorectal cancer.[44] Nonhormonal methods of contraception (e.g., copper IUD) should be considered for women older than 40 years.

Pregnancy

As with all aspects of glomerular disease in women, the pregnancy literature is dominated by SLE with a paucity of data on other primary glomerulonephropathies. A systematic review[45] and meta-analysis data[46] show increased rates of adverse pregnancy outcomes in women with lupus, including preeclampsia (7.6%, RR: 1.91), fetal growth restriction (12.7%, relative risk [RR]: 1.69), preterm delivery (39.4%, RR 3.05), and pregnancy loss due to spontaneous abortion (16.0%, RR: 1.51), neonatal death, and stillbirth (2.5%–3.6%, RR: 1.70). Active lupus nephritis is a significant risk factor for the development of maternal hypertension and preterm delivery,[45,47] and whenever possible, pregnancy should be delayed until disease is quiescent on stable treatment for at least 6 months. However, even a history of lupus nephritis is associated with an increased risk for development of preeclampsia.[45] Other risk factors for the development of pregnancy complications in lupus include black race[48] and Hispanic[49] ethnicity, chronic hypertension,[50] and the degree of proteinuria.[51] The presence of lupus anticoagulant antibodies is a strong predictor of adverse pregnancy outcome in lupus (RR: 8.32; confidence interval: 3.59–19.26),[49] and the presence of antiphospholipid antibodies correlates with rates of hypertension, preterm birth, and pregnancy loss in lupus nephritis.[45] However, most women with quiescent lupus and normal renal function have good pregnancy outcomes.[49]

Published literature regarding the risks of a flare of lupus in pregnancy are conflicting, with significant heterogeneity in disease definition and the level of pre-pregnancy disease activity. A retrospective study of 113 pregnancies in 81 women with lupus nephritis showed a renal flare in 15% of women during pregnancy, as well as in 15% of women within the first postpartum year. This is supported by meta-analysis, which reveals a lupus flare attributable to pregnancy in 26% of women, with nephritis complicating 16% of pregnancies.[45]

The management of lupus nephritis in pregnancy begins pre-pregnancy, with the requirement for disease stability on "pregnancy-safe" medication (see later in this article). Hydroxychloroquine is safe in pregnancy,[52,53] reduces steroid exposure,[54] prevents disease flare,[55] and is associated with a decrease in fetal growth restriction.[56] It should therefore be used during pregnancy in all women with a history of lupus nephritis.[51,57,58] For women with Sjögren syndrome antigen antibodies SSA (Ro) and SSB (La), there is a risk of placental transfer to the fetus, which confers a 2% to 5% risk of congenital heart block and a 15% to 16% risk of cutaneous lupus.[59,60] There is evidence that maternal hydroxychloroquine reduces the risk of congenital heart block in women with a previous affected child,[61] and a reduced frequency of congenital heart block is reported in cohorts with high levels of hydroxychloroquine use.[49] In the absence of better evidence, these data are used to support its use during pregnancy for primary prevention of congenital heart block in women with SSA/SSB antibodies. All women with connective tissue diseases should be screened for these antibodies and, if present, should be offered serial fetal echocardiography from 16 weeks, although the cost-effectiveness of this in women without previous affected pregnancies is unclear.[62] Thrombotic risk should be assessed by maternal antiphospholipid antibody status and quantification of proteinuria in addition to standard criteria. Low molecular weight heparin prophylaxis may be indicated, although there

is insufficient evidence (and consensus) as to the level of proteinuria at which the maternal thromboembolic risk becomes clinically significant. The authors suggest that prophylaxis is considered for pregnant women with a protein:creatinine ratio >250 mg/mmol. Low molecular weight heparin is also indicated during pregnancy for all women with a history of thrombotic or obstetric complications in association with antiphospholipid antibodies. Although there is a strong association between lupus anticoagulant and adverse pregnancy outcome,[49] there are no outcome data to support the use of heparin above that of antiplatelet agents alone in women without previous complications[63]; however, there remain inherent difficulties in assessing the clinical significance of antiphospholipid antibodies in women with lupus nephritis, especially in primiparous women who have no pregnancy history to inform risk assessment. Whether low molecular weight heparin confers additional benefit to the standard use of aspirin in women with lupus nephritis who are positive for lupus anticoagulant remains unknown. The clinical distinction between lupus flare and preeclampsia is difficult given the degree of phenotypic overlap, which includes proteinuria, hypertension, thrombocytopenia, and hemolysis. Although hematuria, quantification of complement, the presence of other distinguishing systemic features, and the use of angiogenic biomarkers (see later in this article) may increase diagnostic specificity, surveillance in pregnancy should be by an expert, multidisciplinary team.

The paucity of disease-specific data for nonlupus glomerular disease was revealed in a systematic review in 2017.[58] IgA nephropathy was most commonly reported in the literature, with 12 studies including a total of 867 pregnancies. In contrast, there are only 2 studies of membranous nephropathy in pregnancy, including 70 pregnancies in 42 women. Although the M-type phospholipase A_2 receptor is the major recognized antigen in membranous nephropathy, data in pregnancy regarding the prognostic and diagnostic utility of anti–phospholipase A2 receptor are limited to an isolated case study of successful pregnancy outcome.[64] Regardless of the glomerular disease etiology, consistent themes include the association of adverse pregnancy outcome with worsening renal function, maternal hypertension, and increasing levels of proteinuria.[58]

Management of nonlupus glomerulopathy in pregnancy is "generic" rather than disease-specific. The importance of disease control in relapsing-remitting glomerular disease is based on the presumption that data from lupus[51] and vasculitis[65] cohorts are generalizable.[58] Blood pressure management is a priority for all glomerular disease, and there is increasing consensus that a blood pressure target of <140/90 mm Hg is appropriate for pregnancy.[9] A recent large randomized controlled trial in women without CKD provides evidence that tighter control of blood pressure during pregnancy does not compromise fetal growth, but does reduce episodes of severe hypertension (>160/110 mm Hg) that would be considered harmful in nonpregnant CKD.[66] Angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists are fetotoxic (see later in this article) and are contraindicated in pregnancy, although there are limited data from single-arm studies, which suggest a pre-pregnancy benefit. Small studies of women with diabetic nephropathy suggest that pre-pregnancy blood pressure control and minimization of proteinuria with angiotensin blockade offers benefit for pregnancy outcome,[67,68] which becomes comparable with women without proteinuria.[69] Low-dose aspirin (75–150 mg) has been shown in a large meta-analysis to reduce the risk of preeclampsia, fetal growth restriction, and preterm birth in women at elevated risk of preeclampsia,[70] and is indicated from 12 weeks' gestation for all women with glomerular disease, regardless of CKD stage.[10] Calcium supplementation also has been shown to reduce the risk of preeclampsia. Meta-analyses of heterogeneous data reveal a reduction in preeclampsia with supplementation of calcium >1 g per day, particularly in women known to be at high risk of preeclampsia, and in those with low dietary calcium intake.[71,72] High-dose calcium supplementation should, however, be avoided in women with renal dysfunction causing secondary hyperparathyroidism.

The Diagnosis of Preeclampsia

There is an increased risk of preeclampsia conferred by all stages of CKD,[73] which increases proportionally with renal disease severity.[32,74] Preeclampsia leads to maternal and fetal morbidity and mortality. It is a key component of adverse pregnancy outcome in CKD, leading to fetal growth restriction and iatrogenic preterm delivery. Although symptoms may be ameliorated, the disease course is unpredictable, and the only cure is delivery. The underlying pathophysiology is believed to be an abnormal vascular response to impaired placentation, leading to multisystem clinical features, including cerebral, hepatic, hematological, renal, and fetal disease. The balance between circulating angiogenic (placental growth factor) and anti-angiogenic markers (soluble fms-like tyrosine kinase) has been found to be altered in women with preeclampsia, with low levels of placental growth factor and high levels of soluble fms-like tyrosine kinase predicting the development of preeclampsia[75] and the need for delivery.[76]

The diagnosis of preeclampsia is made with the development of *de novo* hypertension and proteinuria

after 20 weeks' gestation. Such diagnostic criteria are redundant in women with glomerular disease who have hypertension or proteinuria, or both, that predates pregnancy. The diagnosis of superimposed preeclampsia in women with glomerular disease is therefore difficult, with no standard diagnostic criteria, and the potential for harm due to both under- and overdiagnosis. There are limited data on the predictive and diagnostic utility of angiogenic biomarkers in women with glomerular disease, but isolated cohort studies have shown useful discrimination for superimposed preeclampsia in women with chronic hypertension or CKD using placental growth factor less than the fifth centile in the prediction of delivery within 14 days (negative predictive value 95.5% [95% confidence interval: 89.9–98.5]) in a test cohort and 91.1% [95% confidence interval: 82.6–96.4] in a validation cohort),[77] in addition to a high negative predictive value in ruling out adverse pregnancy outcomes in lupus.[78] More data are needed for interpretation of these biomarkers in women with advanced renal dysfunction.[77,79]

Biopsy

Renal biopsy is indicated when the benefit of obtaining a histological diagnosis outweighs the risk of the procedure. This risk-benefit profile is modified by female reproductive health, which warrants particular consideration (Table 2). For women with lupus nephritis contemplating pregnancy, the threshold for biopsy is potentially reduced. Due to the risks of adverse pregnancy outcome conferred by active disease, this should be excluded or managed before pregnancy, and the value of histological confirmation of disease quiescence should be considered even in the context of low-grade proteinuria and stable renal function, especially if medication needs to be modified before pregnancy.

A systematic review of 197 renal biopsies performed during pregnancy revealed a significantly higher complication rate (7%) for biopsies performed in pregnancy, compared with those performed postpartum (1%).[80] Major bleeding complications were seen in 2% of women, during gestational weeks 23 to 26. Although this study included biopsies taken over a long period (1965–2010), there was no clear trend of a reduction in risk with time. Hypothesized factors contributing to biopsy complications during pregnancy include both the physiological increase in renal blood flow, and the gravid uterus preventing biopsy in the usual prone position. A recent retrospective study showed that biopsy during pregnancy is relatively rare, with only 1% (19/1399) of renal biopsies in women aged 16 to 49 years performed during pregnancy.[81] However, renal biopsy leads to a change in therapeutic management in 66% of pregnant women,[80] highlighting the importance of a histological diagnosis in informing the management of glomerular disease in pregnancy. The major indication for renal biopsy during pregnancy is a *de novo* presentation of apparent glomerular disease in early pregnancy when bleeding risk appears lower, and when a diagnosis would guide therapy. Once the pregnancy reaches beyond 30 weeks' gestation, the increased risks of renal biopsy are unlikely to outweigh the benefits of continuing the pregnancy before proceeding to a lower-risk renal biopsy in the postpartum period. Corticosteroids given at this stage for fetal lung maturation may have additional maternal benefit in steroid-sensitive glomerular disease. The discrimination between glomerular disease and preeclampsia may be more safely resolved by emerging biomarkers, including placental growth factor, soluble fms-like tyrosine kinase, and anti–phospholipase A2 receptor, rather than biopsy.

Biopsy is more commonly performed in the postpartum period than in pregnancy.[81] It is advised to wait for at least 6 weeks for both the clinical and histological features of preeclampsia to regress before assessing the need for biopsy for primary glomerular disease in postpartum women, unless there is clinical suspicion of active or rapidly progressive glomerular disease, in which case biopsy should be done urgently. A retrospective study of 154 biopsies performed within a year of pregnancy in the United Kingdom revealed that the most common diagnosis was focal segmental glomerulosclerosis made in 32% of women, compared with 10% of matched controls. It is difficult to conclude whether this highlights the "unmasking" of asymptomatic renal disease by pregnancy, or the detrimental effect of pregnancy-induced hyperfiltration in women with underlying glomerular dysfunction. The most common diagnosis in women biopsied without relationship to pregnancy was lupus nephritis, which was diagnosed in 24% of women, compared with 14% in pregnancy. This allows the presumption that most pregnant women already had a prior diagnosis of lupus, meaning that treatment could be instigated in pregnancy without repeat biopsy.

Table 2. The impact of reproductive health on indications for renal biopsy in women with glomerular disease

Time of biopsy	Biopsy factors specific to reproductive health
Pre-pregnancy	• Ensures disease quiescence in relapsing-remitting glomerular disease to optimize future pregnancy outcome.
Pregnancy	• To facilitate diagnosis of glomerular disease in pregnancy, where histological diagnosis will alter management. • Increased risk of bleeding in meta-analysis (second trimester).
Postpartum	• Increased prevalence of focal segmental glomerulosclerosis may be due to pregnancy unmasking of asymptomatic disease or causing hyperfiltration injury.

Therapeutic Management

Therapeutic management of glomerular disease includes immunosuppression, angiotensin blockade, antihypertensive treatment, and the management of complications associated with CKD. For all women with glomerular disease, pregnancy intention should be discussed before prescription.

Immunosuppression

Safe and effective contraception should be advised and made available for all women taking teratogenic immunosuppression, including mycophenolate, methotrexate, and cyclophosphamide. These drugs should be avoided in all women who wish to conceive, as well as in women who are at risk of unintended pregnancy. Alternative immunosuppressants, which are considered safe in pregnancy, include steroids,[82–85] calcineurin inhibitors,[86,87] azathioprine,[88–90] and the immunomodulatory drug hydroxychloroquine.[57,61] Substitution of teratogenic drugs should take place at least 3 months in advance of pregnancy to allow an appropriate period of washout, and to establish disease stability on alternate agents. Tacrolimus is an effective treatment for lupus nephritis[91] in uncontrolled studies,[92–94] including pregnancy,[95] small randomized trials,[96,97] and meta-analyses.[98] Although mycophenolate predominates in the management of lupus nephritis outside of pregnancy, it should be remembered that tacrolimus is a valid and safe option during pregnancy, and for women who wish to conceive. Rituximab is actively transported across the placenta during the second and third trimesters. Although use is not associated with congenital malformations, neonatal B-cell depletion can occur, and long-term pediatric outcomes are unknown.[99] Manufacturers therefore recommend avoiding pregnancy for 12 months after exposure. However, rituximab may be the only effective therapy for some women with glomerular disease. For such women, the benefit of controlling active disease in pregnancy must be weighed against the risk of exposure. Use of rituximab immediately before pregnancy or in the first trimester minimizes fetal exposure and the possibility of neonatal B-cell depletion. Live vaccines (Bacillus Calmette–Guérin, rotavirus, varicella) should be avoided for at least 6 months in infants exposed to rituximab *in utero*.

Angiotensin Blockade and Antihypertension Treatment

Angiotensin blockade is fetotoxic in the second and third trimesters, causing oligohydramnios and neonatal renal failure. However, population data regarding angiotensin-converting enzyme inhibitor exposure in the first trimester, when corrected for hypertension and diabetes, shows no increase in the rate of congenital abnormality.[100,101] For this reason, angiotensin-converting enzyme inhibitors can be continued if indicated for glomerular disease until a diagnosis of pregnancy is made, with regular pregnancy testing advocated in women with irregular menstrual cycles. Labetalol, nifedipine, and methyldopa can be safely used for the management of hypertension in pregnancy. Safety data for amlodipine are lacking, but isolated case reports and small cohorts show no evidence of harm.[102–104]

Complications of CKD

Anemia is often multifactorial in women with glomerular disease, including iron deficiency exacerbated by menstrual blood loss and impaired renal synthesis of erythropoietin in CKD. Both oral and i.v. iron[105–109] can be given in pregnancy. The physiological demands for erythropoietin are increased in pregnancy, and gestational use of synthetic erythropoietin may be required at a higher level of renal function than in nonpregnant women. Low-dose aspirin for primary and secondary prevention of vascular disease can be continued in pregnancy, and should be commenced for preeclampsia prophylaxis for all women with glomerular disease (see previously). Vitamin D deficiency is common in pregnancy.[110] In addition, there is a physiological increase in calcitriol ($1,25[OH]_2$-vitamin D) production. For women with renal disease, it is unknown how much this depends on 1-alpha hydroxylase activity in the kidney. In the absence of better evidence, vitamin D replacement should be given if serum calcifediol is <20 ng/ml (50 nmol/l) with continuation of activated forms of vitamin D at the appropriate pre-pregnancy dose.[12] Cinacalcet in pregnancy is discontinued due to insufficient safety data. Systematic review data show that statins are not associated with congenital malformation,[111] although increased rates of pregnancy loss are reported.[112] Current practice is therefore to discontinue statin therapy for the duration of pregnancy. The therapeutic use of hydrophilic statins (pravastatin) in the amelioration of preeclampsia is the subject of ongoing research.[113]

Lactation

Steroids, azathioprine, calcineurin inhibitors, hydroxychloroquine, enalapril, captopril, labetalol, nifedipine, atenolol, amlodipine, aspirin, and synthetic erythropoietin can all be continued during lactation. Up-to-date safety data on specific drugs in breastfeeding is available via the LactMed database (https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm).

Table 3. An overview of the impact of glomerular disease in women

Aspect of health	Glomerular etiology	Impact	Details
Disease prevalence	All	Increased opportunities for diagnosis in women	Higher use of primary care by women, with opportunities for urine and blood pressure screening.
	SLE	Female preponderance	Hypothesized modulation of immune system by sex steroids.
	Preeclampsia	Affects 3%–5% of women	Estimated to be the most common glomerular disease worldwide. Prevalence underestimated by histological data as biopsy is rare.
Fertility	All	Reduced	Effects of CKD on reproductive hormone profile. Voluntary childlessness may contribute.
	SLE	Reduced	Active disease, anti–corpus luteum antibodies, endometriosis, reduced ovarian reserve.
	SLE, vasculitis, rapidly progressive GN	Reduced	Dose- and age-dependent premature ovarian failure secondary to cyclophosphamide. Consider fertility preservation in premenopausal women.
	All	Need for artificial reproductive techniques	Risk of VTE and ovarian hyperstimulation. Single-embryo transfer in CKD.
Contraception	All	Required with teratogenic medication	Includes mycophenolate, cyclophosphamide, methotrexate. Progesterone-only preparations are safe and effective in SLE and CKD.
Pregnancy	All	Remove teratogens in advance of pregnancy	Advise 3 months for washout and to ensure disease stability. CNI, Aza, HCQ, steroids are considered safe for pregnancy.
	All	Adverse pregnancy outcomes	Increased risk with CKD, hypertension, and proteinuria.
	All	Preeclampsia	Prophylaxis with low-dose aspirin (75–150 mg). No diagnostic criteria for superimposed preeclampsia. Clinical overlap with GN signs and symptoms. Surveillance by an expert clinical team. Future use of anti/angiogenic biomarkers predicted.
	All	VTE risk in pregnancy increased if proteinuria	Threshold for LMWH prophylaxis unknown.
	All	BP	Aim $<$140/90 mm Hg.
	All	Vitamin D deficiency	Replacement if 25-hydroxyvitamin D is $<$20 ng/ml (50 nmol/l). Continue activated vitamin D analogs as pre-pregnancy.
	All	Anemia	Increased erythropoietin requirement. May need synthetic replacement.
	All relapsing-remitting GN	Disease activity associated with adverse pregnancy outcome	Aim remission for 6 months before conception. HCQ for all women with lupus nephritis.
	SLE	Risk of flare	Risk of $\sim$15% during pregnancy and $\sim$15% in 1-year postpartum.
	SLE	Placental transfer of maternal antibodies	Risk of neonatal cutaneous lupus and congenital heart block with anti SSA (Ro)/SSB (La). Thromboprophylaxis in antiphospholipid syndrome.
	Membranous	anti-PLA_2R	Role in maternal diagnosis/prognosis and fetal effects unknown.
Long-term outcomes	Membranous and FSGS	Slower rate of decline in renal function	Lower levels of BP and proteinuria in women contribute. Additional protective effect also measured in women.
	All with a history of preeclampsia	Increased future vascular and renal disease risk	Causality versus association not determined.
	IgA	Renal disease progression	Not affected by pregnancy if renal function preserved.

AZA, azathioprine; BP, blood pressure; CKD, chronic kidney disease; CNI, calcineurin inhibitor; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; HCQ, hydroxychloroquine; PLA_2R, anti–phospholipase A2 receptor antibodies; LMWH, low molecular weight heparin; SLE, systemic lupus erythematosus; SSA/SSB, Sjögren syndrome antibodies; VTE, venous thromboembolism.

Long-term Outcomes

There is a lack of consensus in published literature about whether women have a better[114,115] or worse[116] prognosis in glomerular disease, compared with men. Factors that are likely to contribute to this include cohort heterogeneity, a failure to correct for confounding levels of blood pressure and proteinuria, the historical use of creatinine measurement, which skews the diagnosis of CKD toward men,[117] and inaccuracies in determining a change in estimated glomerular filtration rate when values are $>$60 ml/min per 1.73 m^2. A large cohort study found that women with membranous nephropathy (n = 395) and focal segmental glomerulosclerosis (n = 370) had a slower rate of decline in renal function than men.[6] Although this effect was reduced when data were corrected for the lower levels of proteinuria and blood pressure found in women, there was still an apparent protective effect to being female, with higher levels of proteinuria having less effect on disease progression. However, in IgA nephropathy, where there was no significant difference in proteinuria at presentation, there was no gender disparity in rates of renal function decline and adverse outcome.[118]

There is greater consensus in the long-term sequelae attributable to the development of hypertensive pregnancy disorders and preeclampsia. Women who develop preeclampsia have an increased future risk of hypertension,[119,120] cardiovascular events,[121–124] and end-stage renal disease.[125] Large population studies show that women with lupus and a history of preeclampsia are at increased risk of later cardiovascular events,

including mortality.[126] However, the impact of increased postpregnancy surveillance in these populations and the benefits of primary prevention are unknown. For women with glomerular disease, it is unclear whether the development of preeclampsia is an independent risk factor for long-term renal disease progression, or whether preeclampsia is a surrogate marker of underlying renal disease severity. Retrospective data reveal that a combination of pregnancy outcomes, including preeclampsia, preterm delivery, and low birthweight, is associated with accelerated loss of renal function over 3 to 10 years in women with IgA nephropathy only when the estimated glomerular filtration rate is <60 ml/min per 1.73 m^2, or if there is coexisting hypertension or proteinuria >1 g per day.[127] Conversely, cohort studies[128,129] and a meta-analysis[130] show that for women with IgA nephropathy who approximate to CKD Stages 1 and 2, there is no difference in renal disease progression between women who undertake a pregnancy compared with those who do not. Women with IgA nephropathy who have an uncomplicated pregnancy course have been found to have a good renal prognosis, even compared with women who do not undergo a pregnancy following diagnosis.[127]

Conclusions

Glomerular disease in women affects fertility, contraceptive options, and pregnancy outcome, and may modify disease progression, especially in the context of preeclampsia (Table 3). Lupus predominates in published literature and has extra considerations for reproductive health depending on the associated antibody profile. There are fewer disease-specific data for other glomerular etiologies. Pregnancy should be planned for all women with glomerular disease to ensure disease quiescence/stability. Cyclophosphamide, mycophenolate, and methotrexate are teratogenic and should be avoided in women with glomerular disease who wish to conceive, or who are at risk of an unintended pregnancy. Impaired renal function, hypertension, and proteinuria are consistently associated with adverse pregnancy outcome, irrespective of the underlying glomerular etiology. Glomerular disease can mimic preeclampsia, but renal biopsy in late pregnancy is relatively high risk. An important future role for angiogenic biomarkers in the discrimination between glomerular disease and preeclampsia is predicted.

DISCLOSURE

All the authors declared no competing interests.

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REFERENCES

1. O'Shaughnessy MM, Hogan SL, Thompson BD, et al. Glomerular disease frequencies by race, sex and region: results from the international kidney biopsy survey [e-pub ahead of print]. *Nephrol Dial Transplant.* https://doi.org/10.1093/ndt/gfx189. Accessed January 1, 2018.
2. Lu LJ, Wallace DJ, Ishimori ML, et al. Review: Male systemic lupus erythematosus: a review of sex disparities in this disease. *Lupus*. 2010;19:119–129.
3. Murphy G, Isenberg D. Effect of gender on clinical presentation in systemic lupus erythematosus. *Rheumatology (Oxford)*. 2013;52:2108–2115.
4. Margery-Muir AA, Bundell C, Nelson D, et al. Gender balance in patients with systemic lupus erythematosus. *Autoimmun Rev*. 2017;16:258–268.
5. Carter EE, Barr SG, Clarke AE. The global burden of SLE: prevalence, health disparities and socioeconomic impact. *Nat Rev Rheumatol*. 2016;12:605–620.
6. Cattran DC, Reich HN, Beanlands HJ, et al. The impact of sex in primary glomerulonephritis. *Nephrol Dial Transplant*. 2008;23:2247–2253.
7. Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the united states 1980–2010: age-period-cohort analysis. *BMJ*. 2013;347:f6564.
8. Han L, Yang Z, Li K, et al. Antepartum or immediate postpartum renal biopsies in preeclampsia/eclampsia of pregnancy: new morphologic and clinical findings. *Int J Clin Exp Pathol*. 2014;7:5129–5143.
9. Bramham K, Hall M, Nelson-Piercy C, eds. *Renal Disease in Pregnancy*. 2nd ed. Cambridge, UK: Cambridge University Press; 2018.
10. National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and mangement (CG107). Jan 2011. Available at: www.nice.org.uk/guidance/cg107. Accessed January 8, 2018.
11. Wang Y, Hunt K, Nazareth I, et al. Do men consult less than women? An analysis of routinely collected UK general practice data. *BMJ Open*. 2013;3:e003320.
12. Wiles KS, Nelson-Percy C, Bramham K. Reproductive health and pregnancy in women with chronic kidney disease [e-pub ahead of print]. *Nat Rev Nephrol*. https://doi.org/10.1038/nrneph.2017.187. Accessed January 22, 2018.
13. Piccoli GB, Cabiddu G, Daidone G, et al. The children of dialysis: live-born babies from on-dialysis mothers in Italy—an epidemiological perspective comparing dialysis, kidney transplantation and the overall population. *Nephrol Dial Transplant*. 2014;29:1578–1586.
14. Geva E, Lerner-Geva L, Burke M, et al. Undiagnosed systemic lupus erythematosus in a cohort of infertile women. *Am J Reprod Immunol*. 2004;51:336–340.

15. Hickman RA, Gordon C. Causes and management of infertility in systemic lupus erythematosus. *Rheumatology (Oxford)*. 2011;50:1551–1558.
16. Pasoto SG, Mendonça BB, Bonfá E. Menstrual disturbances in patients with systemic lupus erythematosus without alkylating therapy: clinical, hormonal and therapeutic associations. *Lupus*. 2002;11:175–180.
17. Pasoto SG, Viana VS, Mendonca BB, et al. Anti-corpus luteum antibody: a novel serological marker for ovarian dysfunction in systemic lupus erythematosus? *J Rheumatol*. 1999;26:1087–1093.
18. Gupta S, Goldberg JM, Aziz N, et al. Pathogenic mechanisms in endometriosis-associated infertility. *Fertil Steril*. 2008;90:247–257.
19. Boumpas DT, Austin HA, Vaughan EM, et al. Risk for sustained amenorrhea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy. *Ann Intern Med*. 1993;119:366–369.
20. Ioannidis JP, Katsifis GE, Tzioufas AG, et al. Predictors of sustained amenorrhea from pulsed intravenous cyclophosphamide in premenopausal women with systemic lupus erythematosus. *J Rheumatol*. 2002;29:2129–2135.
21. Genest G, Laskin CA. Safety and efficacy of in-vitro fertilization in women with systemic lupus erythematosus and antiphospholipid syndrome. *J Rheumatol*. 2017;44:547–549.
22. Costa M, Colia D. Treating infertility in autoimmune patients. *Rheumatology (Oxford)*. 2008;47(Suppl 3):iii38–iii41.
23. Elizur SE, Chian RC, Pineau CA, et al. Fertility preservation treatment for young women with autoimmune diseases facing treatment with gonadotoxic agents. *Rheumatology (Oxford)*. 2008;47:1506–1509.
24. Somers EC, Marder W, Christman GM, et al. Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. *Arthritis Rheum*. 2005;52:2761–2767.
25. Moore HC, Unger JM, Phillips KA, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. *N Engl J Med*. 2015;372:923–932.
26. Lambertini M, Boni L, Michelotti A, et al. Ovarian suppression with triptorelin during adjuvant breast cancer chemotherapy and long-term ovarian function, pregnancies, and disease-free survival: a randomized clinical trial. *JAMA*. 2015;314:2632–2640.
27. Lambertini M, Ceppi M, Poggio F, et al. Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies. *Ann Oncol*. 2015;26:2408–2419.
28. Office for National Statistics UK. Birth by parents' characteristics in England and Wales 2016. Published 27th Nov 2017. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthsbyparentscharacteristicsinenglandandwales/2016. Accessed January 8, 2018.
29. Orquevaux P, Masseau A, Le Guern V, et al. In vitro fertilization in 37 women with systemic lupus erythematosus or antiphospholipid syndrome: a series of 97 procedures. *J Rheumatol*. 2017;44:613–618.
30. Al-Inany HG, Youssef MA, Ayeleke RO, et al. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. *Cochrane Database Syst Rev*. 2016;(4), CD001750.
31. Piccoli GB, Arduino S, Attini R, et al. Multiple pregnancies in CKD patients: an explosive mix. *Clin J Am Soc Nephrol*. 2013;8:41–50.
32. Piccoli GB, Cabiddu G, Attini R, et al. Risk of adverse pregnancy outcomes in women with CKD. *J Am Soc Nephrol*. 2015;26:2011–2022.
33. Holley JL, Schmidt RJ, Bender FH, et al. Gynecologic and reproductive issues in women on dialysis. *Am J Kidney Dis*. 1997;29:685–690.
34. Yildirim Y, Uslu A. Pregnancy in patients with previous successful renal transplantation. *Int J Gynaecol Obstet*. 2005;90:198–202.
35. Bramham K, Nelson-Piercy C, Gao H, et al. Pregnancy in renal transplant recipients: a UK national cohort study. *Clin J Am Soc Nephrol*. 2013;8:290–298.
36. Schwarz EB, Manzi S. Risk of unintended pregnancy among women with systemic lupus erythematosus. *Arthritis Rheum*. 2008;59:863–866.
37. Trussell J. Contraceptive failure in the united states. *Contraception*. 2011;83:397–404.
38. Petri M, Kim MY, Kalunian KC, et al. Combined oral contraceptives in women with systemic lupus erythematosus. *N Engl J Med*. 2005;353:2550–2558.
39. Estes CM, Westhoff C. Contraception for the transplant patient. *Semin Perinatol*. 2007;31:372–377.
40. Ramhendar T, Byrne P. Use of the levonorgestrel-releasing intrauterine system in renal transplant recipients: a retrospective case review. *Contraception*. 2012;86:288–289.
41. Krajewski CM, Geetha D, Gomez-Lobo V. Contraceptive options for women with a history of solid-organ transplantation. *Transplantation*. 2013;95:1183–1186.
42. Morrison CS, Sekadde-Kigondu C, Sinei SK, et al. Is the intrauterine device appropriate contraception for HIV-1-infected women? *BJOG*. 2001;108:784–790.
43. Mørch LS, Skovlund CW, Hannaford PC, et al. Contemporary hormonal contraception and the risk of breast cancer. *N Engl J Med*. 2017;377:2228–2239.
44. Hunter DJ. Oral contraceptives and the small increased risk of breast cancer. *N Engl J Med*. 2017;377:2276–2277.
45. Smyth A, Oliveira GH, Lahr BD, et al. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. *Clin J Am Soc Nephrol*. 2010;5:2060–2068.
46. Bundhun PK, Soogund MZ, Huang F. Impact of systemic lupus erythematosus on maternal and fetal outcomes following pregnancy: a meta-analysis of studies published between years 2001–2016. *J Autoimmun*. 2017;79:17–27.
47. Bramham K, Hunt BJ, Bewley S, et al. Pregnancy outcomes in systemic lupus erythematosus with and without previous nephritis. *J Rheumatol*. 2011;38:1906–1913.
48. Chakravarty EF, Colón I, Langen ES, et al. Factors that predict prematurity and preeclampsia in pregnancies that are complicated by systemic lupus erythematosus. *Am J Obstet Gynecol*. 2005;192:1897–1904.

49. Buyon JP, Kim MY, Guerra MM, et al. Predictors of pregnancy outcomes in patients with lupus: a cohort study. *Ann Intern Med*. 2015;163:153–163.
50. Imbasciati E, Tincani A, Gregorini G, et al. Pregnancy in women with pre-existing lupus nephritis: predictors of fetal and maternal outcome. *Nephrol Dial Transplant*. 2009;24:519–525.
51. Moroni G, Doria A, Giglio E, et al. Maternal outcome in pregnant women with lupus nephritis: a prospective multicenter study. *J Autoimmun*. 2016;74:194–200.
52. Kaplan YC, Ozsarfati J, Nickel C, et al. Reproductive outcomes following hydroxychloroquine use for autoimmune diseases: a systematic review and meta-analysis. *Br J Clin Pharmacol*. 2016;81:835–848.
53. Sperber K, Hom C, Chao CP, et al. Systematic review of hydroxychloroquine use in pregnant patients with autoimmune diseases. *Pediatr Rheumatol Online J*. 2009;7:9.
54. Clowse ME, Magder L, Witter F, et al. Hydroxychloroquine in lupus pregnancy. *Arthritis Rheum*. 2006;54:3640–3647.
55. Koh JH, Ko HS, Kwok SK, et al. Hydroxychloroquine and pregnancy on lupus flares in Korean patients with systemic lupus erythematosus. *Lupus*. 2015;24:210–217.
56. Leroux M, Desveaux C, Parcevaux M, et al. Impact of hydroxychloroquine on preterm delivery and intrauterine growth restriction in pregnant women with systemic lupus erythematosus: a descriptive cohort study. *Lupus*. 2015;24:1384–1391.
57. Moroni G, Doria A, Giglio E, et al. Fetal outcome and recommendations of pregnancies in lupus nephritis in the 21st century: a prospective multicenter study. *J Autoimmun*. 2016;74:6–12.
58. Blom K, Odutayo A, Bramham K, et al. Pregnancy and glomerular disease: a systematic review of the literature with management guidelines. *Clin J Am Soc Nephrol*. 2017;12:1862–1872.
59. Cimaz R, Spence DL, Hornberger L, et al. Incidence and spectrum of neonatal lupus erythematosus: a prospective study of infants born to mothers with anti-Ro autoantibodies. *J Pediatr*. 2003;142:678–683.
60. Jaeggi E, Laskin C, Hamilton R, et al. The importance of the level of maternal anti-Ro/SSA antibodies as a prognostic marker of the development of cardiac neonatal lupus erythematosus: a prospective study of 186 antibody-exposed fetuses and infants. *J Am Coll Cardiol*. 2010;55:2778–2784.
61. Izmirly PM, Costedoat-Chalumeau N, Pisoni CN, et al. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. *Circulation*. 2012;126:76–82.
62. Andreoli L, Bertsias GK, Agmon-Levin N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. *Ann Rheum Dis*. 2017;76:476–485.
63. Soh MC, Pasupathy D, Gray G, et al. Persistent antiphospholipid antibodies do not contribute to adverse pregnancy outcome. *Rheumatology*. 2013;52:1642–1647.
64. Al-Rabadi L, Ayalon R, Bonegio RG, et al. Pregnancy in a patient with primary membranous nephropathy and circulating anti-PLA_2R antibodies: a case report. *Am J Kidney Dis*. 2016;67:775–778.
65. Fredi M, Lazzaroni MG, Tani C, et al. Systemic vasculitis and pregnancy: a multicenter study on maternal and neonatal outcome of 65 prospectively followed pregnancies. *Autoimmun Rev*. 2015;14:686–691.
66. Magee LA, von Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. *N Engl J Med*. 2015;372:407–417.
67. Hod M, van Dijk DJ, Weintraub N, et al. Diabetic nephropathy and pregnancy: the effect of ACE inhibitors prior to pregnancy on fetomaternal outcome. *Nephrol Dial Transplant*. 1995;10:2328–2333.
68. Bar J, Chen R, Schoenfeld A, et al. Pregnancy outcome in patients with insulin dependent diabetes mellitus and diabetic nephropathy treated with ACE inhibitors before pregnancy. *J Pediatr Endocrinol Metab*. 1999;12:659–666.
69. Nielsen LR, Damm P, Mathiesen ER. Improved pregnancy outcome in type 1 diabetic women with microalbuminuria or diabetic nephropathy: effect of intensified antihypertensive therapy? *Diabetes Care*. 2009;32:38–44.
70. Henderson JT, Whitlock EP, O'Conner E, et al. Low-dose aspirin for the prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive services task force. *Ann Intern Med*. 2014;160:695–703.
71. Hofmeyr GJ, Lawrie TA, Atallah AN, et al. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Syst Rev*. 2014;(6):CD001059.
72. Mackillop L. Pre-eclampsia: reducing the risk with calcium supplements. *BMJ Clin Evid*. 2015;2015:1402.
73. Zhang JJ, Ma XX, Hao L, et al. A systematic review and meta-analysis of outcomes of pregnancy in CKD and CKD outcomes in pregnancy. *Clin J Am Soc Nephrol*. 2015;10:1964–1978.
74. Williams D, Davison J. Chronic kidney disease in pregnancy. *BMJ*. 2008;336:211–215.
75. Agrawal S, Cerdeira AS, Redman C, et al. Meta-analysis and systematic review to assess the role of soluble fms-like tyrosine kinase-1 and placenta growth factor ratio in prediction of preeclampsia. *Hypertension*. 2018;71:306–316.
76. Chappell LC, Duckworth S, Seed PT, et al. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. *Circulation*. 2013;128:2121–2131.
77. Bramham K, Seed PT, Lightstone L, et al. Diagnostic and predictive biomarkers for pre-eclampsia in patients with established hypertension and chronic kidney disease. *Kidney Int*. 2016;89:874–885.
78. Kim MY, Buyon JP, Guerra MM, et al. Angiogenic factor imbalance early in pregnancy predicts adverse outcomes in patients with lupus and antiphospholipid antibodies: results of the PROMISSE study. *Am J Obstet Gynecol*. 2016;214:108.e1–108.e14.

79. Akbari A, Hladunewich M, Burns K, et al. Circulating angiogenic factors in a pregnant woman on intensive hemodialysis: a case report. *Can J Kidney Health Dis*. 2016;3:7.
80. Piccoli GB, Daidola G, Attini R, et al. Kidney biopsy in pregnancy: evidence for counselling? A systematic narrative review. *BJOG*. 2013;120:412–427.
81. Webster P, Webster LM, Cook HT, et al. A multicenter cohort study of histologic findings and long-term outcomes of kidney disease in women who have been pregnant. *Clin J Am Soc Nephrol*. 2017;12:408–416.
82. Källén B. Maternal drug use and infant cleft lip/palate with special reference to corticoids. *Cleft Palate Craniofac J*. 2003;40:624–628.
83. Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. *Teratology*. 1997;56:335–340.
84. Tata LJ, Lewis SA, McKeever TM, et al. Effect of maternal asthma, exacerbations and asthma medication use on congenital malformations in offspring: a UK population-based study. *Thorax*. 2008;63:981–987.
85. Hviid A, Mølgaard-Nielsen D. Corticosteroid use during pregnancy and risk of orofacial clefts. *CMAJ*. 2011;183:796–804.
86. Bar Oz B, Hackman R, Einarson T, et al. Pregnancy outcome after cyclosporine therapy during pregnancy: a meta-analysis. *Transplantation*. 2001;71:1051–1055.
87. Kainz A, Harabacz I, Cowlrick IS, et al. Review of the course and outcome of 100 pregnancies in 84 women treated with tacrolimus. *Transplantation*. 2000;70:1718–1721.
88. Flint J, Panchal S, Hurrell A, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. *Rheumatology (Oxford)*. 2016;55:1693–1697.
89. Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis*. 2016;75:795–810.
90. Ostensen M, Brucato A, Carp H, et al. Pregnancy and reproduction in autoimmune rheumatic diseases. *Rheumatology (Oxford)*. 2011;50:657–664.
91. Mok CC. Calcineurin inhibitors in systemic lupus erythematosus. *Best Pract Res Clin Rheumatol*. 2017;31:429–438.
92. Szeto CC, Kwan BC, Lai FM, et al. Tacrolimus for the treatment of systemic lupus erythematosus with pure class V nephritis. *Rheumatology (Oxford)*. 2008;47:1678–1681.
93. Lee YH, Lee HS, Choi SJ, et al. Efficacy and safety of tacrolimus therapy for lupus nephritis: a systematic review of clinical trials. *Lupus*. 2011;20:636–640.
94. Lee T, Oh KH, Joo KW, et al. Tacrolimus is an alternative therapeutic option for the treatment of refractory lupus nephritis. *Lupus*. 2010;19:974–980.
95. Webster P, Wardle A, Bramham K. Tacrolimus is an effective treatment for lupus nephritis in pregnancy. *Lupus*. 2014;23:1192–1196.
96. Chen W, Tang X, Liu Q, et al. Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide for active lupus nephritis: a multicenter randomized clinical trial. *Am J Kidney Dis*. 2011;57:235–244.
97. Yap DY, Yu X, Chen XM, et al. Pilot 24 month study to compare mycophenolate mofetil and tacrolimus in the treatment of membranous lupus nephritis with nephrotic syndrome. *Nephrology (Carlton)*. 2012;17:352–357.
98. Hannah J, Casian A, D'Cruz D. Tacrolimus use in lupus nephritis: a systematic review and meta-analysis. *Autoimmun Rev*. 2016;15:93–101.
99. Chakravarty EF, Murray ER, Kelman A, et al. Pregnancy outcomes after maternal exposure to rituximab. *Blood*. 2011;117:1499–1506.
100. Li DK, Yang C, Andrade S, et al. Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: a retrospective cohort study. *BMJ*. 2011;343:d5931.
101. Bateman BT, Patorno E, Desai RJ, et al. Angiotensin-converting enzyme inhibitors and the risk of congenital malformations. *Obstet Gynecol*. 2017;129:174–184.
102. Weber-Schoendorfer C, Hannemann D, Meister R, et al. The safety of calcium channel blockers during pregnancy: a prospective, multicenter, observational study. *Reprod Toxicol*. 2008;26:24–30.
103. Gracia PV-D, Dominguez L, Solis A. Management of chronic hypertension during pregnancy with furosemide, amlodipine or aspirin: a pilot clinical trial. *J Matern Fetal Neonatal Med*. 2014;27(13):1291–1294.
104. Morgan JL, Kogutt BK, Meek C, et al. Pharmacokinetics of amlodipine besylate at delivery and during lactation [e-pub ahead of print]. *Pregnancy Hypertens*. https://doi.org/10.1016/j.preghy.2018.01.002. Accessed January 1, 2018.
105. Tariq N, Ayub R, Khan WU, et al. Parenteral iron therapy in the treatment of iron deficiency anemia during pregnancy: a randomized controlled trial. *J Coll Physicians Surg Pak*. 2015;25:193–197.
106. Kriplani A, Mahey R, Dash BB, et al. Intravenous iron sucrose therapy for moderate to severe anaemia in pregnancy. *Indian J Med Res*. 2013;138:78–82.
107. Al RA, Unlubilgin E, Kandemir O, et al. Intravenous versus oral iron for treatment of anemia in pregnancy: a randomized trial. *Obstet Gynecol*. 2005;106:1335–1340.
108. Al-Momen AK, Al-Meshari A, Al-Nuaim L, et al. Intravenous iron sucrose complex in the treatment of iron deficiency anemia during pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 1996;69:121–124.
109. Hladunewich MA, Melamad N, Bramham K. Pregnancy across the spectrum of chronic kidney disease. *Kidney Int*. 2016;89:995–1007.
110. Royal College of Obstetricians and Gynaecologists. Vitamin D in pregnancy: scientific inpact paper No.43. Published 26th June 2014. Available at: www.rcog.org.uk/en/guidelines-research-services/guidelines/sip43/. Accessed January 8, 2018.
111. Karalis DG, Hill AN, Clifton S, et al. The risks of statin use in pregnancy: a systematic review. *J Clin Lipidol*. 2016;10:1081–1090.
112. McGrogan A, Snowball J, Charlton RA. Statins during pregnancy: a cohort study using the general practice

research database to investigate pregnancy loss. *Pharmacoepidemiol Drug Saf*. 2017;26:843–852.

113. Girardi G. Pravastatin to treat and prevent preeclampsia: preclinical and clinical studies. *J Reprod Immunol*. 2017;124:15–20.
114. Neugarten J, Acharya A, Silbiger SR. Effect of gender on the progression of nondiabetic renal disease: a meta-analysis. *J Am Soc Nephrol*. 2000;11:319–329.
115. Coggins CH, Breyer Lewis J, et al. Differences between women and men with chronic renal disease. *Nephrol Dial Transplant*. 1998;13:1430–1437.
116. Eriksen BO, Ingebretsen OC. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. *Kidney Int*. 2006;69:375–382.
117. Jungers P, Hannedouche T, Itakura Y, et al. Progression rate to end-stage renal failure in non-diabetic kidney diseases: a multivariate analysis of determinant factors. *Nephrol Dial Transplant*. 1995;10:1353–1360.
118. Jafar TH, Schmid CH, Stark PC, et al. The rate of progression of renal disease may not be slower in women compared with men: a patient-level meta-analysis. *Nephrol Dial Transplant*. 2003;18:2047–2053.
119. Wilson BJ, Watson MS, Prescott GJ, et al. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. *BMJ*. 2003;326:845.
120. Bokslag A, Teunissen PW, Franssen C, et al. Effect of early-onset preeclampsia on cardiovascular risk in the fifth decade of life. *Am J Obstet Gynecol*. 2017;216:523.e1–523.e7.
121. Wikström A, Haglund B, Olovsson M, et al. The risk of maternal ischaemic heart disease after gestational hypertensive disease. *BJOG*. 2005;112:1486–1491.
122. Bellamy L, Casas JP, Hingorani AD, et al. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ*. 2007;335:974.
123. McDonald SD, Malinowski A, Zhou Q, et al. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *Am Heart J*. 2008;156:918–930.
124. Wu P, Haththotuwa R, Kwok CS, et al. Preeclampsia and future cardiovascular health: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2017;10(2).
125. Kattah AG, Scantlebury DC, Agarwal S, et al. Preeclampsia and ESRD: the role of shared risk factors. *Am J Kidney Dis*. 2017;69:498–505.
126. Soh MC, Dib F, Nelson-Piercy C, et al. Maternal-placental syndrome and future risk of accelerated cardiovascular events in parous Swedish women with systemic lupus erythematosus: a population-based retrospective cohort study with time-to-event analysis. *Rheumatology (Oxford)*. 2016;55:1235–1242.
127. Park S, Yoo KD, Park JS, et al. Pregnancy in women with immunoglobulin A nephropathy: are obstetrical complications associated with renal prognosis [e-pub ahead of print]? *Nephrol Dial Transplant*. https://doi.org/10.1093/ndt/gfx061. Accessed January 1, 2018.
128. Limardo M, Imbasciati E, Ravani P, et al. Pregnancy and progression of IgA nephropathy: results of an Italian multicenter study. *Am J Kidney Dis*. 2010;56:506–512.
129. Su X, Lv J, Liu Y, et al. Pregnancy and kidney outcomes in patients with IgA nephropathy: a cohort study. *Am J Kidney Dis*. 2017;70:262–269.
130. Liu Y, Ma X, Zheng J, et al. A systematic review and meta-analysis of kidney and pregnancy outcomes in IgA nephropathy. *Am J Nephrol*. 2016;44:187–193.