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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

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