Reproductive Issues in Women with Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that primarily affects women during their reproductive years. In the past, epidemiologic relationship between reproductive factors and SLE have been mainly examined in case control studies. A more recent prospective epidemiologic study, has shown potentially important association between oestrogen associated reproductive and menopausal factors and risk of incident SLE among women. Early age at menarche, oral contraceptive use, early age of menopause, surgical menopause and post-menopausal use of hormones were each associated with increased risk of SLE.1

Reproductive issues like menstruation, fertility and pregnancy are important concerns in SLE. In a study by Mandal et al from Eastern India, out of 112 cases of SLE, more than half the cases of had oligo menorrhea or amenorrhea. Doppler studies of the ovaries was an important method to assess gonadal status in SLE, however, this study did not include data on Anti Mullerian hormone.2

Anti-Mullerian hormone (AMH) is expressed by granulosa cells of growing follicles from the stage of primordial follicles to the FSH-dependent phase of antral follicles. AMH is a sensitive marker of ovarian damage due to previous cyclophosphamide (CYC) therapy which remains the treatment of choice of certain severe and refractory manifestations of SLE. Measurement of AMH levels pre-treatment and serially thereafter is useful to guide immunosuppressive therapy along with counselling of patients for ovarian preservation such as treatment with Gonadotrophin releasing hormone analogues and cryopreservation of oocytes/embryos when there is no alternative to CYC.3

Pregnancy is a physiologic condition in which several immune and endocrine changes occur to achieve immunosuppression and tolerance to paternal and foetal antigens. One of the most important immunological modifications during pregnancy is Th1/Th2 cytokine shift. The consequences is that cellular immunity and Th1 cytokine are inhibited whereas humoral immunity, antibody production and Th2 type cytokines are enhanced.4 SLE is considered to be a Th2 type cytokine-driven disease due to the overexpression of Th2-type cytokines. Among these cytokines, interleukin 10 seems to play a central role in the pathogenesis of SLE as well as in disease flare induction.5

The assessment of SLE disease activity is challenging during pregnancy, as many pathophysiological changes in pregnancy may be confused with manifestation of SLE disease activity. Although a number of SLE disease indices have been validated, they possess widely acknowledged flaws, arising in part from the inherent heterogeneity of SLE. For example, the SLE disease Activity Index (SLEDAI) lacks the ability to measure severity of disease activity within an organ system, and indeed omits entire organs such as the gastrointestinal tract. The British Isles Lupus Assessment Group (BILAG) index was developed on the principle of the physician’s intention to treat. It is a transitional index that is able to capture changing severity of clinical manifestations. Over time, several deficiencies were noted by members of BILAG, which prompted a major revision, giving rise to the BILAG-2004 index. BILAG -2004 is a more comprehensive instrument, but a high level of detail renders it cumbersome for use in everyday practice.6

Recently efforts have been made to create pregnancy versions of existing activity Indices to account for pathophysiological changes in pregnancy. In BILAG 2004 pregnancy index majority of the changes were in the glossary, which reminds the physician to differentiate disease activity from pregnancy-related pathophysiological changes such as transient facial blush, melisma/chloasma, bland effusion of knee, mechanical hip/knee pain, and pre-eclampsia/eclampsia, haemodilution of pregnancy and HELLP syndrome. The most significant changes is in the scoring of the renal system, whereby changes in the anti0dsDNA or complement levels are taken into account.7

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consideration in the scoring of proteinuria due to SLE disease activity. 10

Treating to low disease activity is routine in rheumatoid arthritis, but no comparable goal has been defined for SLE. Asia-Pacific lupus collaboration group has recently defined and validated a lupus low disease activity state (LLDAS). This includes the following 1) SLE disease activity index (SLEDAI) ≤ 2K ≤ 4 with no activity in major organ systems (renal and central nervous system (CNS), cardiopulmonary, vasculitis) and no haemolytic anaemia or gastrointestinal activity 2) No new lupus disease activity compared with the previous assessment 3) a safety of previous assessment 4) a current prednisolone National Assessment (scale 0-3) ≤ 4 with no activity in major organ systems (CNS), cardiopulmonary, vasculitis) and no haemolytic anaemia or gastrointestinal activity 2) No new lupus disease activity compared with the previous assessment 3) a safety of Oestrogens Lupus Erythematosus National Assessment (scale 0-3) ≤ 1 4) a current prednisolone (or equivalent) does ≤ 7.5 mg daily ; and (5) well tolerated (or equivalent) does ≤ 7.5 mg daily .

In the present issue of the journal, Gokhale Y and colleagues have addressed the subject of reproductive health in SLE patients focussing only on two issues, menstrual disturbances and pregnancy outcome in 52 cases of SLE seen at a large tertiary care hospital in Western India. 12 This sample size of 52 patients is comparatively large keeping in mind the fact that SLE is an uncommon disease and the typical rheumatology practice has handful of these patients. The strength of this study is the use of validated criteria mainly 1997 ACR criteria for classification of SLE and SLEDAI for assessment of SLE activity.

Limitations of this study should be mentioned. First, this is a single centre study and may have a referral bias. More than half the cases had high disease activity at enrolment and may be due to a fact that a major tertiary hospital receives more severe cases and these may not represent the cases seen in the general population. Second, pregnancy specific SLE disease activity measures have not been studied. Third, there is no mention on the use of serum titres of complement C3/ complement C4 to assess lupus activity during pregnancy. During pregnancy, serum titres of C3 and C4 are usually elevated, so pregnant women with lupus flare may have normal levels of C3 and C4. 13 Fourth, the number patients with APLA syndrome or with Ro and La antibodies during pregnancy is very small for any meaningful interpretation. Last, the data on anti-Mullerian hormone for assessment of menstrual health in SLE is missing.

Recently European League against Rheumatism (EULAR) gathered a multidisciplinary panel to develop an evidence based recommendations for women’s health issue in SLE and or APS. 14 The panel has recommended several points to be considered by the clinicians managing SLE patients. Physicians should be aware of pregnancy physiological changes that can resemble SLE symptoms and sign. Renal activity correlates with adverse pregnancy outcome and should be monitored by means of urine protein excretion, urine sediment analysis (glomerular haematuria, urinary casts) and serum creatinine level / glomerular filtration rate. Serological markers are useful in monitoring SLE activity and the differentiation between pre-eclampsia and SLE disease exacerbation (declining serum C3/C4 levels) even within the normal range) and/or increasing anti-double stranded DNA titres) and preeclampsia.

Future researchers investigating reproductive issues in SLE should use a case control study design, newer imaging techniques for ovarian abnormalities such as ovarian arterial Doppler studies and correlating the same with ovarian hormone levels as well as AMH levels, and use pregnancy specific SLE activity indices for detecting changes in SLE disease activity and diagnosing flares during pregnancy and puerperium.

References