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Review article

New-onset systemic lupus erythematosus during pregnancy: A challenge in diagnosis

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic, multi-organ autoimmune disease that occurs predominantly among reproductive age women. When SLE is newly diagnosed during pregnancy or puerperium, it is known as new-onset SLE during pregnancy. Delayed or missed diagnosis of new-onset SLE during pregnancy due to similar clinical manifestation of SLE with normal physiological changes of pregnancy and lupus nephritis with preeclampsia have drawn attention toward this topic. Furthermore, new-onset SLE during pregnancy has major organ involvement with poor maternal and fetal outcomes. Knowledge and awareness of this complex disease allows physicians to more effectively address and less likely for patient to suffer from misdiagnosis and inappropriate treatment. This article will briefly review important issues in new-onset SLE during pregnancy and describes challenges to overcome its diagnosis.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multi-system inflammation and the presence of circulating auto antibodies directed against self-antigens.[1] SLE is disproportionately high in women 9:1 compared to men.[2–5] The peak of the disease incidence for women appears at their reproductive ages (20–30 years old).[4–6]

Pregnancy complicated with SLE is common and is frequently encountered but literature regarding new-onset SLE during pregnancy is rare.[7] The diagnosis of new-onset SLE is sometimes difficult because the clinical manifestations can mimic those of normal physiological changes of pregnancy. In addition, differentiating active lupus nephritis from preeclampsia is challenging and both of the diseases can also coexist. Literatures on delayed and missed diagnosis due to these reasons have been published.[8,9] Furthermore new-onset SLE during pregnancy was independently associated with poor obstetric complication (OR 7.22, 95% CI 2.14–24.38, $p = 0.001$).[8] Hence, this is a first review which focuses on new-onset SLE during pregnancy and briefly describes challenges to overcome its diagnosis.

2. New-onset SLE during pregnancy

SLE newly encountered at the time when woman is pregnant or in her puerperium is define as new-onset SLE during pregnancy. The 1997 revised classification criteria of the American College of Rheumatology is commonly used as guidelines for SLE diagnosis.[10] The SLE activity during pregnancy is measured by SLE Pregnancy Disease Activity Index (SLEPDAI), Lupus Activity Index in Pregnancy (LAI-P), or modified Systemic Lupus Activity Measure (m-SLAM) published in 1999.[11] Whether the onset of SLE is provoked by pregnancy or not is still conflicting.[12–14] The pathophysiology of SLE disease activity during pregnancy remains unknown. Increased SLE disease activity is expected during pregnancy because of increased levels of estrogen, prolactin and T-helper cell 2 cytokines.[12]

3. Clinical features of SLE

SLE has wide spectrum of clinical manifestations. It includes: constitutional symptoms like fatigue, hair loss, and unexplained fever. Musculoskeletal manifestations like arthritis, arthralgia and inflammatory myositis. Mucocutaneous symptoms such as photosensitive rash (malar rash, discoid rash, sub-acute cutaneous lupus rash), Raynaud's phenomenon, oral/nasal ulceration and alopecia. Cardiopulmonary manifestations commonly involve pleural effusion, pericardial effusion, pulmonary fibrosis and

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rarely involving myocarditis, Libman–Sacks endocarditis and coronary arteritis. Hematological manifestation includes Coombs' positive hemolytic anemia, leucopenia, lymphopenia and thrombocytopenia. Renal manifestations are glomerulonephritis and lupus nephritis. Central nervous system manifestations involve stroke, seizure and coma.

4. Clinical features of new-onset SLE during pregnancy

There are limited numbers of studies in the clinical features of new-onset SLE during pregnancy. The summary of the studies is listed in Table 1.

5. Comparison between clinical presentation of new-onset SLE during pregnancy with flare-SLE during pregnancy and non-pregnant new-onset SLE

Zhao et al.,[15] in their retrospective study focused on clinical characteristics of new-onset SLE during pregnancy or puerperium among 48 patients and compared clinical characteristics with those aged matched new-onset SLE without pregnancy. They reported pregnant patients had lower frequency of fever, arthritis, arthralgia, alopecia, oral ulcer but have higher prevalence of lupus nephritis and thrombocytopenia than the non-pregnant controls with $p < 0.05$.

Yang et al.[16] carried out a case control study that included 155 pregnancy related lupus with 41 new-onset SLE, 41 flare-SLE and 71 stable-SLE with pregnancy and compared them with non-pregnant active female SLE patients. Clinical features of the new-onset SLE with pregnancy and flare-SLE during pregnancy were comparably same except that in new-onset SLE with pregnancy had higher incidence of interstitial lung disease, thrombotic thrombocytopenic purpura and musculoskeletal involvement (arthritis and myositis). But when compared to active SLE non-pregnant patients, new-onset SLE with pregnancy have low musculoskeletal and mucocutaneous involvement but severe disease activity with high renal and hematological involvement supporting Zhao et al.[15] study.

The reason behind high renal and hematological involvement in pregnancy compared to active SLE in non-pregnant group remained unexplained. Lupus-prone animal model studies have also shown estrogen worsened immune-complex glomerulonephritis but improved peri-articular inflammation and focal sialadenitis.[18] In the MRL/lpr mice, repeated pregnancies result in dramatic decline of renal function but improvement of skin diseases.[19] Hence, one should have a careful consideration into the course of SLE disease activity during pregnancy for over expressed renal and hematological diseases.

6. Differentiation of normal physiological changes of pregnancy from active SLE during pregnancy

The recognition of lupus activity during pregnancy may be difficult since the signs and symptoms are similar to those of normal pregnancy. Examples of this apply to most of the organ systems, briefly described as follows.

Chloasma is a dark irregular well demarcated hyper-pigmented macule to patches skin pigmentation affecting up to 75% of pregnant women.[20] Chloasma is commonly found on upper cheeks, forehead, nose and chin (centrofacial pattern); the cheeks and nose (malar pattern); or the ramus of the mandible (mandibular pattern). By contrast, malar rash is a typical localized lesion seen in SLE. Malar rash is an erythematous and/or edematous over the malar eminence with the tendency to spare the nasolabial fold. Both these mucocutaneous clinical features are comparatively

Table 1
Detailed clinical presentations of new-onset SLE during pregnancy according to four different clinical studies.

Author (year)	No. of patients	Mucocutaneous *n* (%)	Musculoskeletal n (%)	Raynaud's phenomenon *n* (%)	Renal *n* (%)	Hematological *n* (%)	Cardiac *n* (%)	Pulmonary *n* (%)	Neuropsychiatric *n* (%)
Zhao C et al. (2013)[15]	48	Malar lesion 17 (35.4) Photosensitivity 1 (2.1) Alopecia 2 (4.2) Ulceration 1 (2.1)	Arthritis 0 (0) Myositis 1 (2.1) Arthralgia 4 (8.3)	2 (4.2)	Lupus nephritis 33 (68.8)	Anemia 37 (77.1) Leucopenia 19 (39.6) Thrombocytopenia 19 (39.6)	Pericarditis 8 (16.7) PAH 4 (8.3)	Pleural effusion 8 (16.7)	1 (2.1)
Yang H et al. (2014)[16]	41	Malar lesion 16 (39) Photosensitivity 5 (12.2) Alopecia 8 (19.5) Oral ulcer 6 (14.6)	Arthritis 12 (29.3) Myositis 3 (7.3)	6 (14.6)	Proteinuria 23 (56.1) Hematuria 19 (46.3) Nephritic syndrome 10 (24.4)	Hemolytic anemia 1 (2.4) Leucopenia 9 (22) Thrombocytopenia 16 (40)	PAH 8 (19.5)	Interstitial lung disease 8 (19.5) Alveolar hemorrhage 2 (49.9)	Central 6 (14.6) Peripheral 1 (2.4)
Xu X et al. (2015)[17]	17	Rash 4 (23.5) Alopecia 1 (5.8)	Arthritis 4 (23.5)	NA	Proteinuria 8 (47) Renal failure 1 (5.8)	Anemia 2 (11.7) Leukopenia 3 (17.6)	PAH 4 (23.5) Heart failure 2 (11.7) Myocarditis 1 (5.8) Pericardial effusion 2 (11.7)	Pulmonary interstitial disease 2 (11.7) Pulmonary interstitial hemorrhage 2 (11.7)	Seizure 2 (11.7)
Chen S et al. (2015)[8]	19	Skin lesion 9 (47.3) Dental ulcer 1 (5.2)	Arthralgia 4 (21)	NA	Proteinuria 18 (94.7) Hematuria 17 (89.4) Nephrotic syndrome 14 (73.6) Renal failure 1 (5.2)	Leucopenia 6 (31.5) Thrombocytopenia 7 (36.8)	Heart failure 4 (21)	NA	NA

Abbreviations: PAH, pulmonary artery hypertension; NA, not available; *n*, number; %, percentage.