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SLE and Pregnancy

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1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects multiple organs. Disease flares can occur at any time during pregnancy and postpartum without any clear pattern.

The hormonal and physiological changes that occur in pregnancy can induce lupus activity. Likewise the increased inflammatory response during a lupus flare can cause significant complications in pregnancy. Distinguishing between signs of lupus activity and pregnancy either physiological or pathological can be difficult [Clowse, 2007].

Pregnancy is a crucial issue that needs to be clearly discussed in details in all female patients with SLE who are in the reproductive age group. There are two essential concerns. The first one is the Lupus activity on pregnancy and the second one is the influence of pregnancy on Lupus. That is the reason why pregnancy should be planned at least six months of remission with close follow-up for SLE flares.

Women with SLE usually have complicated pregnancies out of which one third will result in cesarean section, one third will have preterm delivery and more than 20% will be complicated by preeclampsia [Clowse, 2006; Clark, 2003]. Rarely an SLE patient with a controlled disease activity may deteriorate as pregnancy advances, but still the pregnancy outcome can be better if pregnancy is well timed and managed.

2. Physiology of pregnancy

There are increased demands by the mother, fetus and the placenta during pregnancy which is to be met by the mother's organ systems. Therefore there are some cardiovascular, hematological, immunological, endocrinal and metabolic changes in the mother in normal pregnancy.

2.1 Cardiovascular system

The most important physiological changes that occur in pregnancy are the increase in cardiac output, retention of sodium and water leading to increase in the blood volume, reduction in systemic vascular resistance and blood pressure. These changes begin as early as fourth week of pregnancy [Chapman, 1998], reaching their peak during the second trimester, and then remain relatively constant until delivery. As the increase in the red cell volume is proportionately less than the increase in plasma volume there is hemodilution (physiological anemia) by the end of second trimester [Table 1]. The plasma volume gain is

between 1000ml to 1500ml while the blood volume at term is about 100ml/kg which could commonly present as mild pedal edema [Jansen, 2005]

The increased levels of plasma erythropoietin is responsible for steady increase in the red cell mass by 20-30% who take iron supplements and by 15-20% in those who do not take iron supplements. The physiological anemia that occurs in pregnancy reduces the cardiac work load and helps for better placental perfusion by decreasing the blood viscosity.

It also decreases the risk of thrombosis in utero-placental circulation. The increased blood volume also protects against the usual blood loss in the peripartum period [Stephansson, 2000]. The hemoglobin begins to increase from the third postpartum day and the blood volume returns to non-pregnant level by two months postpartum.

Cardiac output- It increases by 30-50% during normal pregnancy [Robson, 1989]. This is as a result of increase in the preload due to rise in blood volume, decrease in afterload due to decrease in systemic vascular resistance and increase in the maternal heart rate by 15-20 beats/min without any change in the ejection fraction. Twin pregnancy increase the cardiac output by another 20%. However, maternal heart rate, stroke volume, and cardiac output during pregnancy may vary when mother changes from lateral to supine position [Lang,1991, Kametas,2003].

Hemodynamic changes related to labor and delivery – Normal labor and delivery is associated with significant hemodynamic changes due to anxiety, exertion, labor pains, uterine contractions, uterine involution, and bleeding. Cardiovascular effects also occur in some women due to infection, hemorrhage, or the administration of anesthesia or analgesia. The cardiac output and systemic vascular resistance gradually return to non-pregnant levels over a period of three months [Capeless, 1991].

2.2 Hematological changes

The total white cell count is increased up to 40% due to the increase in neutrophils as a result of demargination seen in pregnancy. Therefore the WBC count increases gradually in pregnancy as follows:

1st trimester- 3000-15,000 (Mean increase 9500/mm3)

2nd and 3rd trimesters- 6000-16,000 (mean 10,500)

During labor-may increase up to 30,000/ mm3

The platelet count gradually decreases till the term although they do not fall below 100,000/cu mm, most of the time they are in the lower range of normal values. This is as a result of dilutional effect, increased destruction and turn over.

The RBC increased by 20% due to increased production of erythropoietin but as the plasma volume is increased more than the red cell volume there is a drop in the hemoglobin causing physiological anemia [McColl, 1997].

2.3 Changes in systemic coagulation

Pregnancy is associated with changes in several coagulation factors that result in a 20 percent reduction of prothrombin and the partial thromboplastin times. The main changes are:

- Increased Resistance to activated protein C in the second and third trimesters
- Decreased levels of Protein S
- Increased levels of Factors I, VII, VIII, IX, and X
- Increased Activity of the fibrinolytic inhibitors PAI-1 and PAI-2, although total fibrinolytic activity may not be impaired

PARAMETER IN PREGNANCY	CHANGE (+/-)
Stroke volume	+30%
Heart rate	+15%
Cardiac output	+40%
Oxygen consumption	+20%
SVR (systemic vascular resistance)	-5%
Systolic BP	-10mmHg
Diastolic BP	-15mmHg
Mean BP	-15mmHg
Blood volume	+30%
Plasma volume	+40%
Red blood cell volume	+20%
Renal plasma flow	+35%
Glomerular filtration rate (GFR)	+50%
Polymorphonuclear leukocytes	+40%
Hemoglobin (11 g%)	-1-2G%
Leucocytosis (15,000/cmm)	+40%
Platelet (may drop upto 100,000)	Decreased
ESR (may go up to 40mm/Hr	Increased
Fibrinogen (up to 4.5G %)	+50%
Factor II,III,V,XII	No change
Factors I,VII,VIII,IX,X	Increased
Factors XI,XIII	Decreased
PT & APTT	Reduced
Bleeding time & clotting time	Unchanged
Fibrinolytic activity	Decreased
Complement C3, C4 levels	+10-50%

Table 1. Changes in maternal physiology in pregnancy
(Christopher Ficiliberto & Gertic F.Marx.(1998). Physiological changes associated with pregnancy. Physiology, 9(2):1-3)

The net effect of these pregnancy-induced changes is to produce a hypercoagulable state, which is a double-edged sword, both for protection (e.g., hemostasis contributing to reduced blood loss at delivery) and increased risk (e.g., thromboembolic phenomenon). Venous thrombosis in pregnancy occurs in approximately 0.7 per 1000 women, and is three to four folds higher in the puerpurium than during pregnancy. The risk is increased in women with underlying inherited thrombophilia (e.g. factor V Leiden or the prothrombin gene mutation) [Talbert, 1964; Hellgren, 1981].

2.4 Changes in the maternal immune system

The local adaptation of the maternal immune system is responsible for the successful coexistence between the mother and the fetus/placenta expressing both maternal (self) and

paternal (non-self) genes [Mor, 2009; Robertson, 2010]. The cell- mediated adaptive immune responses are diminished, bypassed or even eliminated but the anti-body mediated immunity is altered while the natural immunity (innate immunity) remains intact which continues to provide the host defense against infection [Nagamatsu, 2010].
During insemination, transforming growth factor β1 (TGF- β1), found in the seminal fluid stimulates the production of granulocyte-macrophage colony- stimulation factor (GM-CSF) and recruitment of inflammatory cell infiltrates in the uterus. During implantation of the fertilized ovum, the majority of the lymphocytes infiltrating the decidua are distinctive uterine natural killer (NK) cells which are CD56++, CD16- & CD3- and express various receptors. Uterine decidua and the feto-placental unit produces large number of cytokines which contribute to shift of the immune response from T helper -1 (Th1) to T helper-2 (Th2) response where cytokines IL-10, IL-4, IL-5,IL-6 and IL-13 predominate while pregnancy rejection is mediated by Th1 response where IFN-α, TNF-β, IL-2, and IL-12 predominate [Lim,2000].
There are many specific mechanisms for immunological protection against the fetus. The most important one is altered HLA expression.

2.4.1 HLA class I
Very specific expression of the HLA class I molecules in trophoblasts is the main factor for protection against paternal HLA class I antigen. The extra-villous trophoblasts (EVT) will not express the HLA class Ia antigens-A, B, C or HLA II antigens but instead they express weak antigens of HLA class Ib – G, E & F which dampen the immune response by interacting with leukocyte inhibitory receptor (LIRs) on uterine natural killer (NK) cells and macrophages and with the T-cell receptors on CD8+ cells [Tilburgs, 2010; Le, 1997; Hunt, 2006).

2.4.2 Natural killer cells
There is a change in the relative population of lymphocytes in the uterus. The T & B cells become scarce and the uterine natural killer (NK) cell population shifts from endometrial NK cells to decidual NK cells.

2.4.3 Progesterone
The role of progesterone, the hormone of pregnancy, seems to be crucial in the maintenance of pregnancy. Progesterone leads to release of progesterone-induced blocking factor (PIBF), which controls cytokine production (IL-10 & others) and NK cell behavior. Increased embryo loss is associated with decreased levels of PIBF & IL-10 and increased levels of IL-12 and IFN-α [Ito, 1995; Nilsson, 1994].

2.5 Hormonal changes in pregnancy
Maternal changes in pregnancy involve hypothalamus, pituitary, parathyroid, adrenal glands, and ovaries to accommodate the needs of the fetal-placental-maternal unit. The hypothalamus still regulates much of the endocrine system through hypothalamic-pituitary axis, directly affecting the function of the above mentioned endocrine organs. Hence an intact hypothalamus is very much essential for normal pregnancy [Chrousos, 1995].

2.5.1 Hypothalamus
Secretes stimulatory hormones like gonadotropin-releasing hormone (GnRH), corticotrophin-releasing hormone (CRH), growth hormone-releasing hormone (GHRH),

thyrotropin-releasing hormone (TRH) and inhibitory hormones like somatostatin and prolactin-inhibiting factors. These hormones are present in high concentrations in portal circulation where they are biologically active and the circulating concentrations of many of these hormones are also elevated in pregnancy due to placental production of identical or variant hormones. The most important changes are seen in the following hormones [Stojilkovic, 1994].

GnRH levels increases during pregnancy whose main source is placenta and plays a main role in placental growth and function. It also produces kisspeptin (KISS-1) which controls the gonadotropic axis and placental kisspeptin gradually increases with pregnancy which has a role in placentation [Bilban, 2004].

CRH from hypothalamus is involved in stress response in pregnancy and delivery. It is also secreted by placenta, chorionic trophoblasts, amnion and decidual cells. The placental CRH do not stimulate ACTH secretion but helps in initiation of labor. Besides CRH the gestational tissues also secretes urocortin which shares the same function of placental CRH, and urocortin-2 (stresscopin- related peptide) and urocortin-3 (stresscopin) which controls the tone of vascular endothelium also play a major role in parturition [Imperatore,2006; Florio, 2007].

2.5.2 Pituitary gland

Changes occur both in the anterior as well as the posterior lobe of pituitary gland.

Anterior lobe of pituitary gland enlarges to 3-fold during gestation due to hypertrophy and hyperplasia of lactotrophs and it takes at least six months after delivery to return to normal volume. FSH, LH & TSH levels are decreased while GH, ACTH & PRL levels are increased (mainly due to placental synthesis) [Lonberg, 2003].

The serum **prolactin** concentration (PRL) increases throughout pregnancy, reaching a peak at delivery to prepare the breast for lactation (figure 1) [Tyson, 1972], though the magnitude of the increase is quite variable.

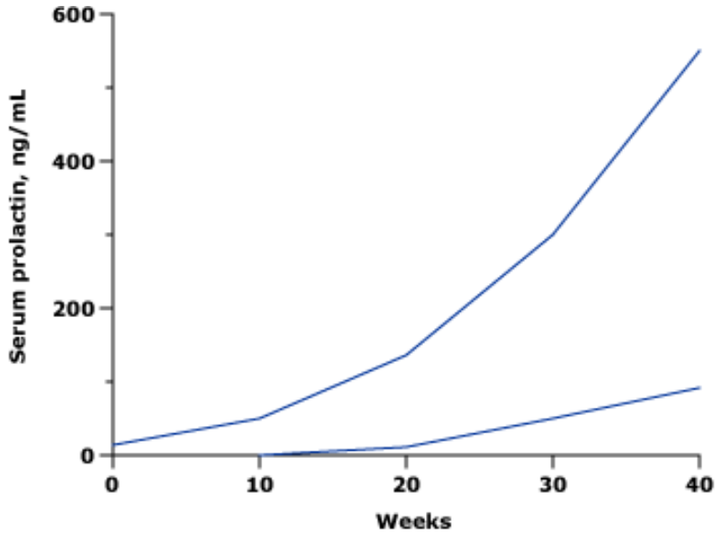

Fig. 1. Serum prolactin concentrations, as a function of time of gestation, showing the increase in prolactin as pregnancy progresses. The zone lines represent the range of values that can be seen. (Tyson, 1972)

The probable cause of hyperprolactinemia is the increasing serum estradiol concentration during pregnancy. By six weeks after delivery, estradiol secretion decreases and the basal serum prolactin concentration returns to normal range as in non-breast feeding mother. In women who are nursing, the decline in serum prolactin level is slower and marked by intermittent hyperprolactinemia related to suckling. Pregnancy appears to permanently reduce pituitary prolactin secretion. The serum prolactin concentration was lower in parous women at up to 12 years postpartum [Musey, 1987].

Posterior lobe of pituitary gland is a storage terminal for antidiuretic hormone (ADH) and oxytocin produced by supraoptic and paraventricular hypothalamic nuclei.

ADH- Its concentration remains in the non-pregnant range throughout pregnancy. Its metabolic clearance is increased due to vasopressinase released by placenta. The plasma sodium concentration falls by 5 meq/ L due to resetting of osmoreceptors as a result of increased levels of HCG.

Oxytocin- Its levels increases gradually throughout gestation and is involved in parturition and lactation [Lindheimer, 1991].

2.5.3 Thyroid gland

The size of the thyroid gland remains the same throughout the pregnancy but there is increase in the thyroxin-binding globulin (TBG). This leads to increased levels of both serum total thyroxin (T4) and triiodothyroxin (T3) but not the physiologically important serum free T4 & free T3 levels [Glinoer, 1990].

2.5.4 Adrenal gland

This gland does not undergo morphological changes during pregnancy. The renin-angiotensin-aldesterone system is stimulated during pregnancy due to decrease in peripheral vascular resistance and blood pressure and progressive decline in vascular responsiveness to angiotensin II. The aldesterone levels increased by 4-6 folds and the blood pressure usually reduced by 10mmHg. Relaxin, which is produced by the placenta, is a vasodilator factor, and aldesterone are critical in maintaining sodium balance in the setting of peripheral vasodilatation. During pregnancy there is increase in the levels of maternal & placental ACTH, cortisol-binding protein, atrial natriuretic peptide (ANP), plasma rennin activity (PRA), sex hormone-binding protein and testosterone levels [Homsen, 1993; Clerico, 1980].

2.6 Changes in the renal system in pregnancy

Both kidneys increase in size by 1 to 1.5 cm during pregnancy. Kidney volume increases by 30 percent, primarily due to an increase in renal vascular and interstitial volume. The renal pelvises and caliceal systems may be dilated as a result of progesterone effects and mechanical compression of the ureters at the pelvic brim. Dilatation of the ureters and renal pelvis (hydroureter and hydronephrosis) is more prominent on the right than the left and is seen in up to 80 percent of pregnant women [Beydoun, 1985]. All the above changes may not resolve until 6 to 12 weeks postpartum. Urinary frequency, nocturia, dysuria, urgency, and stress incontinence are the common symptoms during pregnancy [Nel, 2001].

Renal hemodynamics — Normal pregnancy is characterized by widespread vasodilatation with increased arterial compliance and decreased systemic vascular resistance. These global

hemodynamic changes are accompanied by increases in renal perfusion and glomerular filtration rate. In late gestation, assumption of the left lateral position is associated with increases in glomerular filtration rate and sodium excretion [Almeida, 2009]. The increase in GFR which is approximately 40-50% is mainly due to increased glomerular plasma flow than increased intraglomerular capillary pressure. The renal blood flow increases by 80% above non-pregnant levels. As a result, the serum creatinine and BUN falls below the non-pregnant levels.

The mechanisms for decreased vascular resistance and increased renal plasma flow during pregnancy are not fully understood. Reduced vascular responsiveness to vasopressors such as angiotensin II, norepinephrine, and vasopressin is well-documented. Nitric oxide synthesis increases during normal pregnancy and may contribute to the systemic and renal vasodilatation and the fall in blood pressure [Danielson', 1995].

The ovarian vasodilator hormone, relaxin, appears to be a key upstream mediator of enhanced nitric oxide signaling in pregnancy. Relaxin increases endothelin and nitric oxide production in the renal circulation, leading to generalized renal vasodilatation, decreased renal afferent and efferent arteriolar resistance, and a subsequent increase in renal blood flow and GFR. There is increased urinary protein excretion up to 200 mg/day in the third trimester [Novak, 2001].

3. Distinguishing lupus activity from signs and symptoms of pregnancy

Systemic lupus erythematosus (SLE) primarily affects women in their reproductive years of life, making the issue of pregnancy important to many of these patients. Pregnancy changes affecting disease severity can be attributed to placental or maternal hormones, increased circulation, increased fluid volume, increased metabolic rate, hemodilution, circulating fetal cells, or other factors. Lupus flares are common in pregnancy at rate of 0.06-0.136 per patient-month [Table 2].

Likewise, the increased inflammatory response during a lupus flare can cause significant pregnancy complications. Distinguishing lupus activity from signs of both healthy and pathologic pregnancy is not straight forward and can be very difficult at times [Table 4]. Therefore, activity scales specific for pregnancy which takes into account these issues, have been established. One of them, the Lupus Activity Index in Pregnancy is actually validated, showing high sensitivity, specificity and predictive values for detecting flares during pregnancy [Clowse, 2006].

There is an increase in disease activity during pregnancy, according to many studies. In some patients, this will mean a dramatic worsening of symptoms that can be life threatening. Most patients, however, will have a modest increase in symptoms making pregnancy uncomfortable but not affecting their long-term survival. The increasing levels of estrogens that are seen in normal pregnancy to promote physiologic and immunologic changes required may also increase the lupus activity [Cohen-Solal, 2006; Grimaldi, 2006]. Even though it is highly debated, at least some studies have found a two- to threefold increase in SLE activity during pregnancy [Petri, 1997; Lim, 1995; II Dong, 2011].

40-50% of the patients will have increased SLE activity, majority of which are mild but in 1/3 of cases it may be moderate to severe [Cortes-Hernandez., 2002]. Fortunately, the majority of SLE activity in pregnancy is not severe and in most studies, it is the skin, joint, and constitutional symptoms that are commonly seen. The physiological changes that occur

in pregnancy interfere with assessment of disease activity in SLE. So the signs and symptoms of pregnancy can easily be mistaken for increased lupus activity.
Fatigue can be a distressing complaint throughout normal pregnancy. The fatigue of fibromyalgias increases during pregnancy. As there is no inflammation in this condition the excess sex hormones as well as steroids do not relieve pain.
Palmar erythema and **facial blush** are also seen in pregnancy due to increased secretion of estrogens.

Impact of pregnancy on SLE activity

- Pregnancy probably increases lupus activity:
- About 50% of women will have measurable SLE activity during pregnancy
- Most of the disease activity will be mild to moderate
- 15% to 30% of women will have highly active SLE in pregnancy
- Most common types of SLE activity in pregnancy:
    1. Cutaneous disease (25-90%)
    2. Arthritis (20%)
    3. Hematologic disease (10-40%)

- Risk factors for increased lupus activity:
    1. Active lupus within the 6 months before conception
    2. Multiple flares in the years before conception
    3. Discontinuation of hydroxychloroquin

Table 2. Impact of pregnancy on lupus activity (adopted from Megan, 2007)

Arthralgias, joint effusions, headaches and low back pain are also common in pregnancy due to the effects of relaxin, increased levels of estrogens and fluid retention. The increased **shortness of breath** is due to elevation of diaphragm as a result of upward growth of gravid uterus. The **hair loss** particularly during puerpurium and post-partum is a common finding in normal pregnancy.
The HAQ (Health assessment questionnaire) score increases for normal pregnant women from 0.02 in the first trimester to 0.16 in the second and 0.48 in the third trimester.
As the blood volume increases in pregnancy by 50% there is an effect of hemodilution in the body which **decreases hemoglobin and platelets**, however the hemolytic anemia and platelets less than 100,000/c mm do not occur in normal pregnancy, if present suspect either lupus activity, severe preeclampsia or HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) [Buyon, 1999].
The risk for skin disease during pregnancy is higher (25-90%) than arthritis (20%), thrombocytopenia (10-40%) or nephritis (4-30%). Women with previous history of lupus nephritis have a higher chance for relapse of nephritits (20-30%).
Due to **increased blood volume and glomerular filtration rate** the **serum creatinine falls** gradually and **proteinuria** increases during normal pregnancy. Therefore a stable serum creatinine that is maintained during pregnancy without a fall suggests renal insufficiency. Only proteinuria which is more than double the baseline is to be taken as abnormal, as proteinuria up to 300mg/24 hours can occur in normal pregnancy. A serum creatinine level

>140 μmol/L is associated with a 50% pregnancy loss and this increases to 80% if the level is >400 μ mol/L [Megan, 2007].

Symptoms of pregnancy that can mimic lupus activity	
Constitutional	Fatigue that can be debilitating in entire pregnancy.
Skin	Palmar erythema and a facial blush due to increased estrogen.
Face	Melasma: ''mask of pregnancy.'' A macular, photosensitive Hyperpigmented area over cheeks and forehead.
Hair	Increased hair growth and thickness during pregnancy. Hair loss in the weeks to months postpartum.
Pulmonary	Increased respiratory rate from progesterone. Dyspnea from enlarging uterus late in pregnancy.
Musculoskeletal	Back pain in second and third trimesters. -Relaxin loosens sacroiliac joint and symphysis pubis -Gravid uterus increases lumbar lordosis. Joint effusions: non-inflammatory in lower extremities.
Central nervous system	Headache can be part of normal pregnancy or associated with hypertension. Seizures occur in eclampsia. Cerebral vascular accidents can be caused by preeclampsia or antiphospholipid syndrome.

Table 3. Symptoms in pregnancy that mimics lupus activity
(Adopted from Tsokos GC et al. Systemic lupus erythematosus, A companion to rheumatology. St. Louis: Mosby; 2007)

Complement C3, C4, anti-dsDNA titer, autoimmune target testing (AITT) and lupus activity

The activity of the lupus cannot accurately be assessed by the C3/C4 level and anti-dsDNA titers as in non-pregnant lupus patients. C3 and C4 may be decreased with increased lupus activity because these proteins are consumed in the inflammatory process [Ho A, 2001]. In pregnancy, however, the complement levels may increase 10-50% in response to increased hepatic protein synthesis [Buyon, 1992].
During pregnancy, C3 and C4 may rise to supranormal levels, and thus a flare with complement activation may occur despite apparently normal levels of C3 and C4. Conversely C3and C4 may be low in the absence of a flare, probably due to synthetic defects. However, if C3 or C4 levels drop by >25%, this may be reasonably ascribed to disease activity [Buyon, 1999]. Therefore, the utility of complement measurement in pregnancy is unclear. However, the combination of low complement levels and high-activity lupus leads to a 3-5-fold increase in pregnancy loss and preterm birth [Clowse, 2004].

AITT uses the macrophage cell line (IT-1) as a substrate that is wider than the ANA test in clinical applications

The anti- dsDNA titer is very sensitive for the diagnosis of lupus and can be indicative of increased lupus activity, especially if the kidney is involved [Ho A, 2001]. Increased dsDNA which is considered for diagnosis and increased activity of the disease can be seen in 43% of

pregnant lupus women without disease activity, but rising titers of dsDNA is suggestive of increased lupus activity [Table 4]. However, this antibody does not predict pregnancy outcomes. Instead, the combination of a positive anti-dsDNA titer and highly active SLE contribute toward a 4-6-fold increase in perinatal mortality and a 2-3-folds decrease in full-term birth [Clowse, 2004].

Criteria	For Lupus Flare	
SYSTEM	*"VALID"*	"INVALID"
Cutaneous	Inflammatory rash	Cloasma or Palmar erythema , Post partum alopecia
Musculoskeletal	Inflammatory arthritis	Arthralgias Bland effusion
Hematological	New leucopenia New Thrombocytopenia (PLT <80,000)	Mild anemia ESR up to 40 mm
Serological	Rising titer anti-dsDNA	
Constitutional	Fever not due to infection	Fatigue
Pulmonary	Pain on inspiration	Mild SOB, Hyperventilation 2° to Progesterone
Source: JP Buyon MD	**Rheumatologia**	**2(4) 199 (2004)**

Table 4. Criteria for lupus flare

LE cell phenomenon is seen in lupus patient's blood. LE cell test was the first autoimmune disease test of using this phenomenon that showed lower sensitivity and specificity. So HEp-2 cell using the conventional antinuclear antibody (ANA) test is currently being used as a standard test. However AITT uses the macrophage cell line (IT-1) as a substrate that is wider than the ANA test in clinical applications.

The ESR is unreliable in pregnancy because it increases significantly in normal pregnancy but if it is very high (>40mm/hr) it can be taken for increased lupus activity. In non-pregnant SLE patients, CRP may increase with a lupus flare. The use of CRP has not been systematically tested in SLE pregnancies [Ho A, 2001]. As CRP is not elevated in pregnancy, it is to be considered for increased activity of the disease. Therefore elevated CRP is a better indicator for increased lupus activity than elevated ESR [Ruiz, 2004; Megan, 2007].

In a study (Table 5), complement C3 levels were statistically significant in hematuria, leucopenia, hypertension, high serum CRP levels, and preterm premature rupture of membranes. Complement C4 levels were statistically significant in kidney disease status, hematologic diseases and admissions to NICU. Anti-dsDNA was statistically significant in oligohydramnios, elevated CRP and neonatal anti-SSB (La) antibody detection. It is helpful to predict neonatal diseases. AITT is statistically significant in high ESR values and Apgar score. This helps to predict state of the newborn immediately after birth [Il Dong Kim, 2011].

Complement C3	Complement C4	Anti-dsDNA	AITT
Leucopenia	Hematological disease	Anti-SSB/La antibodies (in neonates)	
Elevated CRP		Elevated CRP	Elevated ESR
Hypertension	Proteinuria		
Hematuria	Hematuria		
Premature rupture of Membranes (PRM)	Admission to NICU	Oligohydramnios	1 & 5 minute Apgar score
AITT= Auto-immune	Target Testing		

Table 5. Correlation of pregnancy complications with C3, C4, Anti-dsDNA and AITT
Source: II Dong Kim et al. Korean J Obstet Gynecol 2011; 54:17-25

In conclusion, although it is difficult to differentiate lupus activity from changes that occur in pregnancy, one needs to consider carefully all the above factors in a lupus pregnancy with high clinical suspicion of active disease for the diagnosis of increased lupus activity.

4. Influence of pregnancy on SLE

SLE patients suffer from different kinds of pregnancy related complications more than non-SLE women. The following are the common pregnancy related complications.

4.1 Hypertension

Blood pressure levels tend to drop during pregnancy starting from the first trimester and increases at term. Hypertension complicates 5% to 7% of all pregnancies. About 25% of lupus patients will develop hypertension and proteinuria in the second-half of pregnancy. In case of prior nephropathy of any type, hypertension develops in 41% of patients during pregnancy [How, 1985]. Pre-existing hypertension is the most common predisposing factor for preeclampsia.

The risk of preterm birth, IUGR, and fetal loss, all increase in hypertensive pregnant lupus patients. Yasmeen, et al identified 555 deliveries in women with SLE and compared those pregnancy outcomes with outcomes in control group of 600,000 deliveries in women without SLE. The results showed that women with SLE had higher rates of adverse outcomes of pregnancy, including hypertensive complications, preterm delivery, cesarean delivery, IUGR, and fetal deaths, than did women without SLE. The rate of hypertensive disorders of pregnancy were found to be 2.9% as compared to the controlled population which is only 0.4% [Yasmeen, 2001]. Hypertension can present in pregnancy as

- Pregnancy-induced hypertension or gestational hypertension (blood pressure $\geq$ 140/90mmHg seen first time during pregnancy, returns to normal levels 12 weeks post partum)
- Chronic hypertension (blood pressure $\geq$ 140/90mmHg before pregnancy or diagnosed before 20 weeks of gestation or hypertension first diagnosed after 20 weeks of gestation and persistent after 12 weeks post partum)
- Preeclampsia (blood pressure $\geq$ 140/90mmHg after 20 weeks of gestation with proteinuria of $\geq$ 300mg/24hrs)
- Eclampsia (preeclampsia with seizures)

4.2 Lupus flares

There is conflicting data on whether SLE activity increases during pregnancy. The risk of lupus flare is increased if the woman has had active lupus in the last 6 months of pregnancy. Therefore, inactive disease at the onset of pregnancy provides optimum protection against the occurrence of flare during pregnancy [Urowitz, 1993].

Lupus may flare during any trimester of pregnancy or post partum period. The flares are usually mild mainly involving the joints, skin and blood. Some of the physiological changes of pregnancy can mimic the symptoms of the active disease such as palmar erythema, arthralgia, myalgia and lower limb edema [Table 4].

High prolactin levels, presence of lupus anticoagulant and increased SLE activity, have poor outcome in pregnancy [Jara, 2007a]. Oral Bromocriptine may play a role in the prevention of maternal-fetal complication such as premature rupture of membrane, preterm birth and active disease as reported in one of the clinical trials but this needs to be confirmed by further trials [Jara, 2007b].

The most important laboratory data to differentiate lupus flare in pregnancy from pregnancy changes include rising titer of anti-double strand DNA antibodies, presence of red blood cell casts in the urine, positive direct Coomb's test and presence of antiplatelet antibody with thrombocytopenia. Complement levels can be in normal range as complement levels increases during pregnancy due to estrogen-induced hepatic synthesis of complements.

In normal pregnancy the increased glomular filtration rate observed in the second trimester leads to increase in proteinuria. Thrombocytopenia is seen in pregnancy, although it is generally mild and occurs only in 8% of women [Burrow, 1988]. The lupus activity index in pregnancy (LAI-P) scale which is a modified activity scale specific for pregnancy, studied by Ruiz-Irastorza G, et al showed (LAI-P) high sensitivity to changes in lupus activity, and has a significant correlation with modified physician global assessment (M-PGA). This index has high sensitivity, specificity, predictive values, and likelihood ratios for diagnosing SLE flares during pregnancy and puerpurium [Riuz, 2004].

4.3 Preeclampsia

SLE in general and hypertension and/or renal disease in particular were agreed upon by most studies to increase the risk for preeclampsia [Clowse, 2007]. Patients with class III and IV SLE nephritis have a significantly higher prevalence of preeclampsia (28% to 38%) as compared to class II or I (11.1%) or to lupus controls without nephritis (4.6%).

It is important to differentiate isolated preeclampsia from lupus nephritis during pregnancy, as the corner stone in preeclampsia management is delivery of the fetus. Preeclampsia as we mentioned previously is blood pressure levels of over 140/90 along with proteinuria of > 300mg per 24 hour after 20 weeks gestation [Table 6]. Sometimes it can be associated with features of HELLP syndrome. If preeclampsia presents very early (< 20 weeks) one should look for the presence of APS (Antiphospholipid antibody syndrome). Very severe cases of PET may evolve into eclampsia.

In patients with no previous history of renal involvement and with normal baseline urinary parameters, preeclampsia is strongly supported by the onset of proteinuria in the third trimester, new onset hypertension, inactive urinary sediment, absence of anti-DNA antibodies and normal complements levels.

PARAMETER	ACTIVE LUPUS NEPHRITIS	PREECLAMPSIA
High BP	Present or Absent	Diastolic BP > 90 mm Hg
Proteinuria	• >500 mg/24 hr if normal at baseline • Doubling if >500 mg/24 hr at baseline • Occur before 3rd trimester	• >300 mg/24 hr if normal at baseline • Occur during 3rd trimester
Edema	Present / Absent	Present / Absent
Active Sediment	Present / Absent	Absent
Uric Acid	Normal or Elevated	Elevated
C3, C4	Low	Normal
Anti-ds DNA Abs	Rising	Absent

Table 6. Broad Guidelines to differentiate Lupus Nephrites from Preeclampsia (Buyon, 2004)

Antiplatelet agents during pregnancy, particularly the use of low dose Aspirin as primary prevention in PET are associated with moderate but consistent reduction in the relative risk of premature birth before 34 weeks gestation, and of having a pregnancy without serious adverse outcome [Askie, 2007]. A systemic review showed that Aspirin reduces the risk of perinatal death and preeclampsia in women with a history of risk factors such as preeclampsia, chronic hypertension, diabetes, and renal disease. Given the importance of these outcomes and the safety along with low cost of aspirin, low dose aspirin should be considered in all women with the above risk factors [Coomarasamy, 2003]. Previous studies have suggested that several factors, including pre-existing hypertension, renal insufficiency, presence of APS, and active SLE, may increase the risk of preeclampsia in pregnancies complicated by SLE [Mascola, 1997]. The features which differentiate preeclampsia from lupus nephritis are given in Table 6.

4.4 Lupus Nephritis (LN)

Pregnant women with long-standing LN are at risk of spontaneous abortions and increased perinatal mortality. However, the outlook of pregnancy in patients with stable LN at conception is relatively favourable. Remission in lupus nephritis has been defined as stable renal function, a serum creatinine within the normal range, urinary red cells below 5/high power field, proteinuria below 0.5g/day and normal serum C_3 levels for the last 12-18 months (Table 6) [Gayed, 2007].

The incidence of obstetric complications and maternal mortality is high in patients with active lupus nephropathy associated with pre-existing hypertension. Pregnant women with LN require intense fetal and maternal surveillance for a better outcome of pregnancy [Rahman, 2005]. The increase in proteinuria can be secondary to the usual increase in glomerular filtration rate observed in the second trimester of pregnancy. Moderate renal impairment at the onset of pregnancy, as reflected by serum creatinine level of 120μmoles/L or greater, has a greater decline in renal function than would be expected in a non-pregnant patient for a similar time period [Hou, 1985].

The fetal loss in patients with active LN in pregnancy occurs in 36% to 52% of the pregnancies, as compared to fetal loss in pregnant patients with history of LN but with stable creatinine and minimal proteinuria during pregnancy, which is only 11% to 13% [Huong, 2001; Moroni, 2002]. A study of 24 pregnancies in 22 women with LN noticed

flares in 50% with proteinuria, 42% with hypertension, and 25% with preeclampsia [Soubassi, 2004]. Lupus nephritis flare can be associated with other evidence of active lupus such as serositis, arthritis, and high titers of anti-DNA antibodies. The proteinuria of preeclampsia decreases after delivery but not that of active lupus patient.

4.5 Thrombocytopenia

It is not unusual to see this in pregnancy. It is encountered in at least 8% of all pregnancies. In gestational thrombocytopenia, the degree of thrombocytopenia is usually mild, with no history of bleeding or preconception history of thrombocytopenia. The platelet count usually returns to normal within 2-12 weeks post partum [Jeffrey, 2002]. Also, thrombocytopenia may occur for a variety of reasons in pregnancy such as SLE, APS, HELLP or medication particularly Heparin or expanding of circulatory volume.

4.6 Other complications

Pregnant lupus patients can face other problems like HELLP syndrome (**H**emolysis **E**levated **L**iver enzymes and **L**ow **P**latelets) and Gestational diabetes [Joya, 2010, Josephine, 2006].

5. Influence of SLE on pregnancy

5.1 Effect on fertility

Systemic lupus erythematosus (SLE) is not known to affect the fertility directly and therefore SLE patients are as fertile as any other female in general population [Kamashta, 1996]. Lowered fertility rate is seen in patients with active disease on high dose steroids, patients with established renal disease and moderate to severe renal failure [Hou, 1975]. End-stage renal disease secondary to lupus nephritis can result in amenorrhea, although amenorrhea in renal patients may also be due to ovarian failure secondary to cyclophosphamide or of auto-immune origin [Kong, 2006].

5.2 Effect of flare on conception

SLE patients can experience disease flare at anytime during pregnancy with potential negative effects on the conception. Lupus flares occur more during pregnancy and post partum period in SLE patients than non-SLE pregnant patients [Petri, 1991]. Increased lupus activity is seen after pregnancy in 1/3 of cases [Seng, 2008]. Therefore, for better outcome of lupus pregnancy it is essential to control disease activity and achieve clinical remission at least 6 months before pregnancy [Georgion, 2000].

Exacerbations or relapses occur during the course of pregnancy and immediate post partum period in 25% to 60% of cases. However, the likelihood of increased clinical activity of SLE during pregnancy is influenced by signs of activity present at onset of pregnancy. In the absence of signs of clinical activity for at least 6 months before conception, relapses occur only in one-third of cases, whereas in patients with clinical activity at onset of pregnancy, persistent activity or exacerbations occur in approximately two-thirds.

Fetal survival in these patients parallels with the incidence of SLE activity: Hence fetal survival is seen in 85% to 95% in the group with inactive disease at conception and 50% to 80% in subjects with active disease at the onset of pregnancy [Weyslett, 1991]. More recent studies have shown a 2-3 fold increase in SLE activity during pregnancy [Rehman, 2005]. Adverse live-birth outcome was significantly associated with low pre-gestational serum

albumin level, elevated gestational anti-ds DNA antibody, and diabetes mellitus. Spontaneous abortion was directly associated with low levels of pre-gestational serum albumin, positive anticardiolipin IgA, anti-B_2-glycoprotein IgM, and anti-La antibodies.

Complication	Moderate to severely active SLE (n=57)	Inactive or mildly active SLE (n=210)	P-value
Miscarriage	7%	7%	0.9
Stillbirth:	16%	5%	<0.01
Extreme Preterm (<28 weeks gestation)	17%	6%	0.09
Late Preterm (28 to 37 weeks gestation)	49%	26%	<0.001
Small for gestational age baby (<10th percentile weight for gestational age)	30%	21%	0.23

Table 7. Increased Lupus Activity in Pregnancy Increases Pregnancy Complications
(*Data from* Clowse MEB et al. The impact of increased lupus activity on obstetric outcomes. Arthritis Rheum, 2005. 52(2): p. 514–21)

5.3 Effect of lupus nephritis

The obstetric complications and maternal mortality is high in patients with active lupus nephropathy associated with pre-existing hypertension [Rahman, 2005]. Pregnant women with long-standing lupus nephritis are at high risk of spontaneous abortions and increased perinatal mortality. However, the outlook of pregnancy in patients with stable lupus nephritis at conception is relatively favorable [Table 7]. Patients with the combination of either high clinical activity of SLE and low complement or positive anti-ds DNA had the highest rate of pregnancy loss and preterm birth [Clowse, 2011].

Female recipients transplanted for renal failure secondary to lupus nephritis can maintain pregnancy successfully. Outcomes are comparable to renal recipients with other diagnoses. Newborns in both groups were often premature and had low birth weight [McGrory, 2003]. The second trimester Doppler ultrasound examination is the best predictor of late pregnancy outcome in systemic lupus erythematosus and/or the anti-phospholipids syndrome [Lethi, 2006].

Management of pregnant women with renal disease involves awareness of physiological changes such as decreased serum creatinine and increased proteinuria. Worsening proteinuria may be due to lupus flare but differential diagnosis also includes preeclampsia. In fact, women with severe renal impairment (serum creatinine over 300µmols/L) have a chance lower than 30% of having successful pregnancy [Germin, 2006].

5.4 Effect of Antiphospholipid Syndrome (APS)

Anti-phospholipids antibodies (APL), which include lupus anti-coagulant (LAC), anti-cardiolipin antibodies (ACL), and B_2glycoprotein are frequently found in patients with SLE, and their presence has been associated with increased fetal loss. If APL are present, the fetuses are susceptible to placental insufficiency. APL but not anti-Ro and anti-La

Term	Definition
Spontaneous abortions or miscarriages	Pregnancy loss <20 weeks of gestation
Recurrent abortion or recurrent miscarriages	≥3 spontaneous abortions
Fetal loss	Pregnancy loss from 10 weeks of gestation and onwards
Intrauterine fetal demise (IUFD) or stillbirth	Fetal death occurring at ≥20 weeks of gestation
Fetal wastage	Sum of spontaneous abortions and stillbirths
Neonatal death	Infant born live but died up to 28 days after birth
Small for gestational age	Birth weight <10th percentile
Low birth weight	Birth weight <2500 g
Very low birth weight	Birth weight <1500 g
Preterm birth or prematurity	Gestational age <37 weeks

Table 8. Adverse pregnancy outcomes
(Data from Josephine P et al-Lupus and pregnancy: complex yet manageable
Clin Med Res 2006 Dec; 4(4):310-321)

antibodies might have a role in direct placental damage. The levels of β-hCG are reduced in women with history of recurrent pregnancy loss or thromboembolic events. High titers of APL were found to cause the largest reduction in β-hCG. Anti-Ro and anti-La did not induce placental damage [Schwartz, 2007]. APL also have direct effect on trophoblast possibly through exposed anionic phospholipids and/ or adherent B_2glycoprotein "B_2GP1", resulting in altered trophoblast intercellular fusion, gonadotropin secretion and trophoblast invasiveness [Di Simone, 2005].

Typical fetal loss secondary to APS is characterized by progressive intrauterine growth restriction (IUGR) ultimately leading to fetal death [Birdsall, 1996]. Both early and late fetal deaths are associated with APS [Rai, 1995]. The live birth of an APS pregnancy rate increased from 19% in untreated patients to 70% in treated patients [Lima, 1996]. The risk of pregnancy loss in women with anti-phospholipids antibodies (APL) and with a previous pregnancy loss has been estimated at over 60%. APS pregnancy is not without complications in the mother [Table 9].

Beside those already mentioned, pregnancy confers a higher risk of thrombosis in women who are already at increased risk or with a past history of thrombotic events [Branch, 1992]. The incidence of extensive infarction, decidual vasculopathy, decidual thrombosis and perivillous fibrinoid change, which have been thought to be characteristic lesions of APS placenta, was significantly higher in LAC, or ACL or both LAC & ACL positive patients than in the patients without APL. LAC and ACL double-positivity is an important risk factor for fetal death in the SLE patient [Petri, 2004; Ogishima, 2000].

As the placenta positive for IgG-APL showed pathogenic findings such as infarction, degeneration, thrombus formation and fibrinoid deposits, it is suggested that IgG-APL

bound to the placental tissue might cause direct pathologic damage to the placenta which results in IUFD, or IUGR by uteroplacental insufficiency [Katoro, 1995].

Fetal Risks	Maternal Risks
• Recurrent miscarriage (first and second trimester)	• Thrombosis
• Intrauterine growth restriction	• Severe early onset preeclampsia
• Fetal death	• Preterm labour, rupture of membranes
• Premature delivery	• Worsening of pre-existing thrombocytopenia
• Congenital malformations/ intracerebral haemorrhage (If Warfarin is administered)	• Placental abruption • Other bleeding complications

Table 9. Obstetric risks associated with anti-phospholipid syndrome
(Adapted from S Stone, MA Khamashta, and L Poston [Stone, 2001])

Fetal risk had been reduced progressively in the past 40 years. Although it still continues to be higher than that occurring in pregnancies of healthy women. The presence of APL considerably worsens the fetal outcome [Moroni, 2005]. It is suggested that patients with early-onset severe preeclampsia be screened for APL, if antibodies are detected, then these women should be considered for prophylactic anticoagulation therapy [Branch, 1989].
A retrospective case-control study of 242 pregnancies in 112 patients concluded that the risk of fetal loss in SLE is 2.5 times higher than that in the normal population. The presence of LAC indicated a high risk of fetal loss, while the absence of APL is an indication of a favorable pregnancy outcome. No individual APL test seems to be clearly superior to the others to detect patients at high risk for fetal loss. However, by combining ACL with LAC, a reasonably good sensitivity and specificity can be achieved. Regardless of APL, infants of women with SLE are born more prematurely and are more retarded in growth than the infants in the normal population. Thus, factors other than APL also contribute to the adverse fetal outcome in lupus pregnancy [Heikki, 1993].

5.5 Effect of anti-ro/and or anti-la antibodies

SLE is the most recognized Rheumatic disease in which auto antibodies, anti-Ro and/or anti-La can pass from the mother to the fetus across the placenta during pregnancy. Anti-Ro/SSA antibodies are associated with neonatal lupus but do not negatively affect other gestational outcomes, and the general outcome of these pregnancies is now good. A large multi-centers cohort prospective controlled study of 100 anti-Ro/SSA positive women concluded that anti-Ro/SSA antibodies are responsible for congenital heart block but do not affect other outcomes of pregnancy, both in SLE and non-SLE women.
The general outcome for these pregnancies is now very good, if prospectively followed by multidisciplinary teams [Antonio, 2011; Brucato, 2002], although various studies considered the anti-Ro/SSA antibody as a possible causative factor for unexplained pregnancy loss. A significant greater fetal wastage is seen in black anti-Ro (SSA) positive women as compared to black anti-RNP positive women. No significant difference in fetal wastage was noted between the white SLE and the non-SLE women in either antibody group. These data suggest that black SLE patients with anti-Ro (SSA) antibody may be at increased risk of fetal

wastage [Watson, 1986]. Hull et al reported three SLE patients with anti-Ro/SSA and a history of spontaneous abortions [Hull, 1983].
Ro52, Ro60 and La IgG antibodies all are transferred from the mothers to their fetus in utero and were present in the infant at birth as detected by enzyme-linked immunosorbent assay using recombinant antigens and a synthetic peptide. A significant decrease in Ro52, Ro60 and LA IgG auto antibody levels the infants was observed from birth to 4-5 weeks of the age. Ro- and La-specific IgA and IgM antibodies were detected in the serum from a subset of mothers. However, Ro- and La-specific IgA and IgM antibody levels were low or non-detectable in children raised both with and without breastfeeding. These findings support a role for placental materno-fetal transfer of the IgG auto antibodies in the pathogenesis of neonatal lupus erythematosus (NLE) and indicate that refraining from breast-feeding does not protect from NLE skin involvement [Klauinger, 2009].
Studies focusing on the neuropsychological development of SLE offspring show an increased number of learning disabilities in children with normal intelligence levels. The presence of anti-Ro/La antibodies and disease activity (flare) in mothers during pregnancy were significantly related to higher prevalence of learning disabilities in offspring. Mainly sons of women with SLE were significantly more likely to have learning disabilities than daughters of women with SLE or children of either sex in the control group as these maternal antibodies likely affect the fetal brain of male offspring and result in later learning problems. These findings should promote greater awareness and early educational intervention in those children [Ross, 2003].

5.6 Other risks

Prospective studies indicate that the majority of lupus mothers can sustain pregnancy without detrimental effects, provided that the pregnancy is planned during the inactive phase of the disease. Nevertheless the fetal risk, although progressively reduced during the last 40 years, continues to be higher, particularly in patients with anti-phospholipids antibodies (APL), than in pregnancies in healthy women [Moroni, 2003].
Premature rupture of membranes (PROM) is more common in pregnancies occurring in women with SLE which is the major etiology for preterm births [Johnson, 1995]. SLE is associated with increased risk of spontaneous abortion (pregnancy loss prior to 20 weeks gestation), preeclampsia, stillbirth (pregnancy loss after 20 weeks gestation), premature rupture of membrane (PROM), intrauterine growth restriction and fetal death.
The risk of thrombosis, infection, thrombocytopenia and requirement for transfusions is higher in women with SLE. Lupus patients also have a higher risk for cesarean sections, preeclampsia, and are also more likely to have other medical conditions like diabetes, hypertension, and thrombophilia which are also associated with adverse pregnancy [Clowse, 2008].
SLE women belong to category of high-risk pregnancy. Highly active lupus during pregnancy leads to increased premature birth and a decrease in live births, with almost one-quarter of these pregnancies resulting in fetal loss. The Hopkins Lupus Center Database has identified a combination of two factors: high clinical activity and serologic activity. These two are very important factors which predict preterm birth. Pregnancies in lupus patients must be closely watched and treated during all the three trimesters to improve pregnancy outcomes [Urowitz,1993; Chandran, 2005].

6. Conclusion

SLE is a chronic multisystem disease occurring in young women in their childbearing age. And therefore, the collaboration of rheumatologist and obstetrician who are experienced in high risk pregnancies management, are essential for managing these women with lupus who becomes pregnant to have a successful outcome as these women already have high risk in terms of fetal loss and spontaneous abortions [Georgion, 2000]. The manifestations of normal pregnancy can be mistaken as signs of lupus activity making the diagnosis and treatment challenging. Therefore, understanding of pregnancy and lupus interaction has resulted in better methods of monitoring and treating this particular clinical situation.

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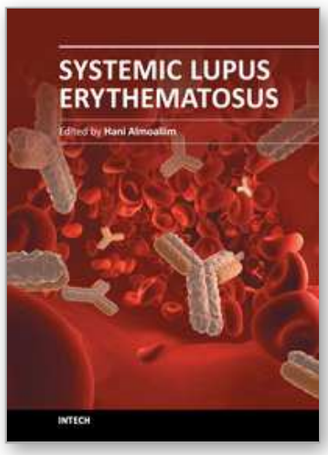

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This book provides a comprehensive overview of the basic and clinical sciences of Systemic Lupus Erythematosus. It is suitable for basic scientists looking for detailed coverage of their areas of interest. It describes how advances in molecular biology have increased our understanding of this disease. It is a valuable clinical resource for practicing clinicians from different disciplines including rheumatologists, rheumatology fellows and residents. This book provides convenient access to information you need about cytokines, genetics, Fas pathway, toll like receptors and atherogenesis in SLE. Animal models have been reviewed as well. How to avoid delay in SLE diagnosis and management, in addition to various clinical manifestations including pregnancy and SLE have all been explained thoroughly in this book.

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