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Management of Pregnant Lupus

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1. Introduction

The initiating point to manage pregnancy in lupus patient is ideally before the onset of pregnancy. Therefore, at preconception counseling, the physician not only estimates the risk profile of the patients but also reviews their drugs. This is to avoid known teratogenic drugs, to discontinue certain medications and to initiate other drugs as a golden goal to protect the mother and fetus from adverse effects of these medications. Hence, it is essential to observe the mother at least six months before attempting conception for a better outcome in lupus pregnancy.

The management of SLE pregnancy should be a multidisciplinary approach and needs good coordination and follow-ups with experts in the field like rheumatologist, obstetrician who is experienced in dealing with high risk pregnancies and nephrologist if the renal impairment is also present. Therefore, all lupus pregnancies should be closely monitored.

This chapter covers general guidelines for the management of SLE during Pregnancy and post partum period in addition to safety of contraceptive methods in lupus women.

2. Management issues

Once the pregnancy test results are positive we should have a baseline evaluation of the disease activity, its severity and major organ involvement [Table1].

- Prenatal care visits: Every 4 weeks up to 20 weeks, then every 2 weeks until 28 weeks, then weekly until delivery.

SLE presents several challenges in managing a pregnant woman and her fetus, as SLE affects almost every organ system in the body and shows a broad spectrum of disease manifestations ranging from mild to life-threatening conditions [Boumpas, 1995].

Due to the improvement of treatment modalities more and more women with this disease are able to become pregnant. Pregnancy outcomes have improved dramatically over the last 40 years, with a decrease in pregnancy loss rate from a mean of 43% in 1960-1965 to 17% in 2000 - 2003 [Clark, 2005].

Pregnant patients with SLE on immunosuppressive therapy need prophylaxis for infection, (including antibiotics for invasive procedures), and immunization with influenza & pneumococcal vaccine.

FIRST TRIMESTER	• Baseline CBC, electrolytes, serum creatinine, liver enzymes, uric acid.
	• Fasting blood glucose, fasting lipid profile if at high risk, for example if patient is nephritic or on steroids
	• Normal antenatal check up
	• ANA, Anti-DsDNA, anti-Ro and anti-La, antibody titers
	• Complements levels (C_3,C_4,CH_{50})
	• Anticardiolipin antibodies, lupus anticoagulant and β_2 glycoprotein
	• Urinalysis, 24-hour urine collection for measurement of protein and creatinine clearance
SECOND TRIMESTER	• Baseline laboratory studies
	• Anti-DsDNA
	• Complements levels (C_3,C_4,CH_{50}) , urinalysis
	• Obstetric ultrasound: Every 4 weeks from 20 weeks of gestation until delivery "to monitor fetal growth"
	• Mother with positive Anti-Ro and/or Anti-La antibodies, serial fetal echocardiography between 16-36 weeks of gestation
THIRD TRIMESTER	• Repeat laboratory studies
	• Urinalysis, 24-hour urine protein collection if proteinuria is present
	• Weekly fetal non-stress test (NST) and/or biophysical profile (BPP) scoring from 28 weeks gestation
	• Fetal Doppler ultrasonography to be done in presence of intrauterine growth restriction
EACH VISIT	• Careful blood pressure measurement
	• Urine dipstick for proteinuria

Table 1. Guidelines for assessment of pregnant patients with lupus

2.1 Safety of medications

SLE is common in women of childbearing age. Physicians should be aware of which medications to be used safely at preconception & conception, and effects on infants exposed to certain drugs.

The Food and Drug Administration (FDA) has a classification system for pregnancy risk (Table 2). The pharmacological management of SLE is challenging as it has an unpredictable clinical course, with the variable organ system involvement and the lack of clear understanding of disease pathogenesis [Francis L, 2009].

2.1.1 Antihypertensive drugs

Hypertensive disorders of pregnancy are the leading cause of maternal mortality and morbidity. Blood pressure tends to decrease in the first and second trimesters of pregnancy. The most appropriate blood pressure threshold and goal of antihypertensive treatment are controversial. For women with severe hypertension (defined as a sustained systolic BP of $\geq$160mmHg and/or a diastolic BP of $\geq$ 110mmHg), there is consensus that antihypertensive therapy should be given to lower the maternal risk of central nervous system complications. The target BP of safety in Pregnancy is less than 140/90 mm of Hg.

United States FDA Pharmaceutical Pregnancy Categories	
Pregnancy Category A	Adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
Pregnancy Category B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.
Pregnancy Category C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Pregnancy Category D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Pregnancy Category X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Table 2. United States FDA pharmaceutical pregnancy categories

The bulk of evidence relates to use of parenteral hydralazine or labetalol, and oral nifedipine, labetalol or methyldopa [Magee, 2011]. It is essential to keep the blood pressure in the normal range. Patients with new onset hypertension in pregnancy should be evaluated for PET. The medications that are best studied are methyldopa and labetalol. Methyldopa is the only antihypertensive agent for which there has been long-term follow-up of children exposed in utero [Antonio, 2011].
Angiotensin converting enzyme inhibitors and angiotensin receptor blockers should be avoided prior to conception as they are contraindicated and cannot be considered safe. And these drugs are also associated with higher incidence of fetopathy [Cooper, 2006].

2.1.2 Aspirin

Treatment with low doses of Aspirin during pregnancy would be indicated in women with SLE, APS, hypertension, history of preeclampsia, and renal disease. Aspirin can cross the placenta and can cause congenital anomalies in animals but these are rare in human beings. Several large prospective studies failed to confirm a significant increase in cleft palate or congenital anomalies [Jick, 1981]. Low dose of Aspirin is safe throughout pregnancy. Women who took Aspirin had a significantly lower risk of preterm delivery than those treated with placebo but there is no significant difference in perinatal mortality [Kozer, 2003].
A meta-analysis showed reduction in the risk of preeclampsia, preterm delivery before 34 weeks of gestation and serious adverse outcomes among women taking low-dose Aspirin or dipyridamole [Aski, 2007].

Aspirin has anti-prostaglandin effects and therefore it is better discontinued 8 weeks prior the expected delivery to avoid prolonged gestation and labour. This also reduces bleeding during delivery and bleeding complications in the fetus.

2.1.3 Non-steroidal anti-inflammatory drugs (NSAIDs)

The effect of NSAIDs use on the fetus depends upon the term of pregnancy. A number of cohort studies looking at the teratogenic risk of NSAIDs use during the first trimester have not found an increased risk of congenital malformation [Janssen, 2000]. However, due to the shared property of inhibition of prostaglandin synthesis, adverse effects such as constriction of the ductus arteriosus in utero, persistent pulmonary hypertension, renal dysfunction in the neonate, increased maternal blood loss, and prolongation of pregnancy & labour are possible when administered to pregnant patients. NSAID should be given in the lowest effective dose, and should be withdrawn before 8 weeks of expected date of delivery [Ostensen, 1994].

Prostaglandins (PGs) increase uterine contractions, enhance platelet aggregation and increase the fetal renal blood flow. Therefore, NSAIDs by inhibiting the PG synthesis, may decrease the fetal urinary output. NSAIDs, by inhibiting cyclooxygenase, decrease the PG synthesis.

If NSAID is clinically indicated in the first or second trimester, Ibuprofen would be the preferred one.

NSAIDs can potentially inhibit contractions and thereby prolong gestation. Because of the later effect, indomethacin, a potent NSAID, has been used in the treatment of premature labour. NSAID inhibition of fetal urinary output may cause oligohydramnios and this is reversible once the NSAID is stopped. Inhibition of prostaglandin synthesis by NSAID may also result in constriction of the ductus arteriosus which can cause fetal pulmonary hypertension. In the studies with indomethacin, these effects were first noticed in the 27th week of gestation but most marked in the 32nd week of gestation [Janssen, 2000; En Hams, 2002].

2.1.4 Anti-malarial drugs

Hydroxychloroquine: "HCQ" is the commonest anti-malarial drug used in SLE. It has been used in pregnancy for malarial prophylaxis with no teratogenic effects [Lewis, 1973].

HCQ main mechanism of action is through inhibition of antigen processing and inflammatory cytokine release [Fox, 1996]. These drugs are highly effective for discoid lupus erythematosus (DLE) cutaneous lesions. HCQ improves photosensitive skin lesions and prevents lupus flares [Gladman, 1998]. Studies have shown that HCQ can prevent renal and central nervous system lupus. It also exhibits the role of a prophylactic agent against some of the major morbidities of SLE and its treatment, namely hyperlipidemia, diabetes mellitus and thrombosis [Mpetvi, 1996].

As it has a long half life of eight weeks and accumulates in the body, discontinuation of drug immediately after conception does not prevent the exposure of fetus to the drug. A systemic review of hydroxychloroquin use in pregnant patients with auto-immune diseases from 1980 to 2007 showed that HCQ is not associated with any increased risk of congenital defects, spontaneous abortions, fetal death, prematurity or decreased number of live births in patients with auto-immune disease [Sperber, 2009].

RA Levy et al observation in prospective randomized placebo controlled study revealed that HCQ can be used safely in pregnancy with additional benefits on the disease activity.

The neonatal results (Apgar score, weight and gestation age) were significantly better in the HCQ group with absence of teratogenic effects after 3 years of follow-up in children [Levy, 2001].
HCQ is often needed to manage hyperactivity of the disease, as it appears to be safe and decreases lupus activity during pregnancy.

2.1.5 Corticosteroids

It is relatively safe to use during pregnancy but we should pay attention to maternal hypertension, gestational diabetes, infection, weight gain, acne and proximal muscle weakness. Therefore close monitoring with the use of the lowest possible dose of corticosteroid needed to control disease flare along with vitamin D and calcium supplements. Although animal studies have suggested an increased risk of oral clefts associated with glucocorticoid, several human studies have failed to demonstrate either teratogenic or toxic effects [Raybum, 1992].
Corticosteroids (Prednisalone, Prednisone, and Methylprednisolone) are metabolized by placenta II-beta-hydroxy steroid dehydrogenase (II-beta-HSD) which converts active cortisone to inactive cortisone. Therefore, fetal blood levels are approximately 10% of the mother's level [69], while fluorinated corticosteroids (dexamethasone and betamethasone) do cross the placenta in an un-metabolized form. Therefore, neonates should be monitored for evidence of adrenal insufficiency.
If our concern is to treat the mother, the most suitable corticosteroid is prednisalone, prednisone or methylprednisolone. But if our concern is to treat the fetus, then it is either dexamethasone or betamethasone, which is not inactivated by placental 11-beta hydroxysteroid dehydrogenase and are best suited for fetal treatment as they clearly reduce the risk of death and respiratory distress syndrome in the preterm infants [NICHHD, 1994].
It is currently recommended that obstetricians give only a single course of antenatal corticosteroids to pregnant women to enhance lung maturity instead of giving repeated doses as weekly courses of antenatal corticosteroid which did not reduce composite neonatal morbidity compared with a single course of treatment. Weekly courses of antenatal corticosteroids should not be routinely prescribed for women at risk of preterm delivery [Guinn, 2001].
Separate meta-analysis of the data in the Cochrane review showed that betamethasone and not dexamethasone reduces neonatal morbidity [Crowley, 2000] as betamethasone may offer better long-term neuro developmental outcome for the fetus [Lee BH, 2008].
In patients with chronic corticosteroid treatment during pregnancy, "stress doses" of hydrocortisone are recommended for prolonged labor, delivery, caesarian section, or any emergency surgery.

2.1.6 Immunosuppressive agents

Cyclophosphamide

Fetal survival is strongly in doubt when cyclophosphamide is required to treat lupus during pregnancy. The high risk for loss of the fetus should be discussed with the patient prior to administration of cyclophosphamide [Clowse MEB, 2005]. Patients undergoing therapy with cyclophosphamide must avoid pregnancy during therapy, especially in the first trimester. Attempts of conception should be delayed until three months after cessation of therapy.

It is a teratogenic drug and should only be used after the first trimester unless the mother's life is threatened [Briggs, 2005]. To avoid fetal loss and malformations from inadvertent first trimester exposure during cyclophosphamide therapy, strict adherence to birth control measures, as well as a pregnancy test prior to pulse therapy should be the routine practice [Clowse MEB, 2005].
In patients with life-threatening disease, the use of cyclophosphamide may be considered after the first trimester.

Azathioprine (AZA)

It is a purine analogue which interferes with the synthesis of nucleic acid. Although azathioprine crosses the placenta, only minimal amount reaches the fetal blood. Azathioprine metabolites 6-thioguanine nucleotide (6-TGN) was slightly lower in the RBC of the infant than the mother, while other azathioprine metabolite 6-methylmercaptopurine (6-MMP) could not be detected in the infant which means the placenta forms a (relative) barrier to AZA and its metabolites [Da Boer, 2006].

Methotrexate (MTX)

It is contraindicated in pregnancy (FDA risk category x) because of severe adverse effects on both the fetus and the course of the pregnancy [Janssen, 2000]. Plan for conception should be taken after three months of methotrexate withdrawal as the active metabolites remain in the body for approximately two months after its discontinuation. MXT acts as a folate antagonist and therefore leads to folate depletion during MTX treatment. Hence folate supplementation should be continued throughout pregnancy.

Mycophenolate mofetil (MMF)

It is mainly used in renal lupus, and there are very few data concerning its use. It is advisable to switch to azathioprine before conception.MMF currently used as a maintenance therapy for lupus nephritis, and also used for resistant skin lupus, lupus disease activity and hematological manifestations [Karim, 2002].
Based on toxicity shown in animal studies, patients should not become pregnant while taking MMF. Women taking MMF who wish to become pregnant should discontinue the drug at least 6 weeks prior to conception.

Cyclosporine (CSA)

Cyclosporine is an immunosuppressant that was first used for pregnant transplant rejection. CSA does not appear to be a major human teratogen. It may be associated with increased rate of prematurity [Bar, 2001].

2.1.7 Biologic agents

Anti-tumor necrosis factor alpha (Anti-TNFα)

Maternal immunoglobulin (IgG) concentrations in fetal blood increase from early second trimester through term as maternal antibodies transported across the placenta to protect the new born. Most antibodies are acquired during the third trimester. The three commercially available TNF-α inhibitors (infliximab, etanercept, adalimumab) constructed based on IgG, so that these can cross the placenta to the fetus in the first trimester and more efficiently during the second and third trimesters.
Anti-TNFα medications have led to improvements in the treatment of inflammatory conditions. The safety of these drugs during pregnancy is an important issue. Prospectively

collected data appear to be reassuring. However, an analysis of the FDA-reported anomalies has raised some questions. It appears that significant levels of these drugs cross the placenta as the pregnancy nears term, but very little passes into the breast milk. Prior to usage of these medications during pregnancy, their risks and benefits, other treatment options, and the ongoing inflammatory conditions, all must be carefully weighed by both doctor and patient [Clowse, 2010].

The FDA classified these biological agents as pregnancy risk category B, which means that no adverse pregnancy effect have been observed in animals studies but there have been insufficient controlled human studies. The published experience with anti-TNF during pregnancy consists of a limited number of case reports, series, and ongoing registry data.

Many patients have experienced successful pregnancies following TNF exposure. Patients with unplanned pregnancies exposed to TNF inhibitors either before or after conception does not require termination of pregnancy unless additional maternal-fetal assessments suggest untoward or dangerous effects. While most of the existing data on TNF inhibitors use in pregnancy have been generated during conception and the first trimester of pregnancy, there is limited and inadequate information regarding their use throughout pregnancy or during breast feeding [Ali, 2010]. At present the use of biological agents cannot be recommended throughout pregnancy [Sorensen, 2011]. Therefore, it is better to stop anti-TNF once the pregnancy test is positive.

Rituximab

It is a chimeric anti-CD_{20} monoclonal β-cell depleting antibody. One should continue to counsel the women to avoid pregnancy for up to 12 months after rituximab exposure [Chakra Varty, 2011]. Therefore, it must be withdrawn before a planned pregnancy. Experience with rituximab during pregnancy is too limited to allow any statement on safety in pregnancy. When administered in the second and third trimester, β-cell depletion occurs in the fetus. Long-term studies on β-cell and immune function of children exposed in utero are lacking [Ostensen, 2008]. Rituximab is potentially unsafe because of reversible fetal cytopenias including β-cell depletion have occurred in infants of mothers who are given this drug during pregnancy [Doria, 2008].

2.1.8 Other therapeutic measures

Intravenous Immunoglobulin (IVIG)

During pregnancy, intravenous Immunoglobulin (IVIG) may be used if needed to control severe maternal lupus activity. It does not appear to cause any fetal abnormalities. This drug has been used for many years without any adverse effects [Bonnie, 1995]. In a study comparing twelve SLE-suffered pregnant patients from recurrent spontaneous abortion (RSA) treated with a high dose of IVIG as against twelve SLE-RSA pregnant patients treated with prednisalone and NSAIDs showed a beneficial clinical response following IVIG treatment in all patients, and the antibodies and complement levels also tended to normalize in most of the patients. So IVIG is considered safe and effective [Perricone, 2008].

Plasmapheresis (PP)

It is safe, expensive, labor-intensive procedure. Its absolute indications include hyper viscosity, cryoglobulinemia, pulmonary hemorrhage and TTP. PP may be useful in cyclophosphamide resistant and serious organ–threatening disease [Erickson, 1994;

Wallance, 2001]. It is safe in children and pregnant females [Wallance, 2001]. Removal of anticardiolipin antibodies or Lupus anticoagulant by plasmapheresis during pregnancy or its use in those with recurrent thromboembolic episodes has been the subject of numerous case reports but no prospective studies have been done. However, it is believed that plasmapheresis during pregnancy definitely removes anticardiolipin antibodies. [Koblayash, 1992].

Aphaeresis is well tolerated among pregnant patients, and has been used to remove antiphspholipid antibodies and Anti-Ro (SSA). It has been suggested that weekly Plasmapheresis can decrease anti-52 kD reactivity and might prevent heart block if it is initiated in the first trimester [Vonderleij, 1994].

2.2 Delivery

Systemic lupus erythematosus is not an indication for delivery by cesarean section; although high rates of preeclampsia and cesarean section in connective tissue disease pregnancies were documented in a population based study they mainly emphasized on the importance of monitoring and obstetrical interventions [John Fredrick, 2000].

A team approach guarantees to the pregnant women with SLE, a safe vaginal delivery and allows performing a cesarean section for obstetric indications only.

In a study of 555 lupus pregnancies, cesarean sections were needed in 38.2% of these patients versus 19.7% of controls [Yasmeen, 2001] .The major indications for cesarean section are fetal distress and maternal preeclampsia. One should remember that, general anaesthesia in a pregnant women has a mortality rates of 16.7% which is much greater than that of epidural or subarachnoid anesthesia [Hawkins, 1997]. It is ideal that the obstetrician, the anesthesiologist and the rheumatologist should evaluate the condition of the mother and the fetus and plan the type of delivery accordingly.

Generally , in the case of vaginal delivery the anesthesiologist can guarantee an epidural analgesia with no greater risks than those of a healthy parturient. In the event of cesarean section we can usually administer a neuro-axial anesthesia as the preferred type of anesthesia reserving the general anesthesia only to obstetrical emergencies [Rawetz, 2004]. The indications for cesarean section include maternal causes such as avascular necrosis of the hips with inadequate hip abduction, placental abruption or fetal causes such as fetal distress, prolapsed umbilical cord, abnormal non- stress test, cephalo-pelvic disproportion and transverse presentation. Delivery should be in a hospital which has neonatal intensive care unit. Pregnant women with lupus treated with systemic steroid within two years of the anticipated delivery should receive steroid stress coverage during delivery.

2.3 Puerpurium

The optimum management is not over with the birth of a healthy baby. In fact, postpartum period should be considered as a high risk for pregnant lupus patients with several possible complications ahead. First, the mother can suffer a lupus flare, since several studies have confirmed the postpartum period is particularly high risk for increased lupus activity. A close surveillance in the first four weeks after delivery is thus warranted, especially in women with recent activity or with a previous history of severe disease. However no specific prophylactic therapy, such as increasing the dose of steroid, is recommended.

The puerpurium has also high risk for thromboembolic complications. This is especially true in women with APS, in whom adequate thrombo-prophylaxis with low molecular weight

heparin (LMWH) should be extended 4-6 weeks after delivery. Those with previous history of thrombosis can be back on their usual full anticoagulant therapy within first 2-3 days postpartum. It should be remembered that both warfarin and heparin are safe during lactation [Guillermo Ruiz-Irastorza et al, 2009].

2.4 Lactation

The increasing prevalence of breast feeding along with the increased frequency of pregnancies in females with chronic medical conditions have increased the number of patients who face possible harmful effects on the newborn of medication excreted in breast milk. Generally, drugs known to be extensively protein bound are excreted in breast milk to a lesser extent than drugs that are poorly bound to plasma proteins.

Factors related to breast milk
Milk composition (lipid and protein concentrations)
Factors related to the mother
Renal and hepatic excretion Dose and duration of treatment Route of administration
Factors related to the infant
Age Drug Absorption Renal and hepatic excretion Volume of milk intake Safety of the drug for the infant
Factors related to the drug
Solubility in water and lipid Molecular size Oral bioavailability Toxicity Suppressive effect on milk production Long-acting drug x short-acting drug

Table 3. Factors that determine the safety of the drugs used during breastfeeding. (Adapted from Howard & Lawrence, 1999.)

There are multiple factors that determine the concentration of the drug in breast milk which include maternal, infant, and drug-related factors [Bowes, 1980] as shown in the table (Table 3). It is recommended to take the medication immediately after breastfeeding the baby, to ensure least possible concentration of the drug in breast milk. Safety of medication is very important during lactation.

2.4.1 Aspirin

Nursing mothers should avoid large doses of Aspirin. The American Academy of Pediatrics recommends that Aspirin be used cautiously by the mother of the nursing infant and large doses of it should be avoided [Pediatrics, 1994].

2.4.2 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

The American Academy of Pediatrics considers Ibuprofen, Indomethacin, and Naproxen to be compatible with breastfeeding [Pediatrics, 1994], although most NSAIDs do not achieve high concentrations in breast milk [Ostensen, 1996]. Ibuprofen presents extremely low level in breast milk and has very short half-life; therefore it is considered to be a reasonable choice as an analgesic in the lactating women.

2.4.3 Hydroxychloroquin (HCQ)

The amount of HCQ received by children through lactation seems to be very low. HCQ should probably be maintained throughout pregnancy in patients with SLE as it is also safe in breastfeeding [Cosedoat, 2005]. The American Academy of Pediatrics classifies the drug as compatible with breastfeeding. Excretion into breast milk was very low (0.2mg/kg/day) and this level is not thought to be toxic [Costedoat, 2002]. Drug levels in milk reached a peak 2 hours after ingestion of hydroxychloroquine and declined after 9 hours. It was estimated that a nursing child would ingest between 0.06-0.2mg/kg/day or approximately 2% of the mother's weight-adjusted dose [Notionn, 1984; Ostensen, 1985]. Routine eye exams of breastfed children are not indicated as the follow-up studies of exposed children are re-assuring [Costedoat, 2002].

2.4.4 Corticosteroids

Corticosteroids do not enter breast milk in large quantities. The American Academy of Pediatrics has declared prednisone and prednisalone as safe and compatible with breastfeeding. Infant exposure to prednisalone through breast milk can be minimized by dosing prednisalone at infrequent intervals and avoiding nursing for at least 4 hours following a dose [Alan Kamada, 1994] as peak milk steroid levels occurred approximately 2 hours after a dose of prednisalone. No data are available on the use of dexamethasone or betamethasone in lactating women.

2.4.5 Cyclophosphamide

Lactation is contraindicated during cyclophosphamide use as it is found in substantial concentrations in human breast milk [Wiernik, 1971]. Patient with life-threatening condition, who received cyclophosphamide during second or third trimester, their offspring should be monitored for immunosuppression and the development of secondary malignancies.

2.4.6 Azathioprine (AZA)

Nursing is not recommended in patients on AZA, because of the long-term potential of immunosuppression and carcinogenesis [Pediatrics, 1994], although, there were no reports to confirm this. A report on a series of 4 patients treated with azathioprine while lactating, the breast milk samples were analyzed for 6-mercaptopurine (6-MP) in 2 of the mothers. Levels of 6-MP were undetectable. Therefore, relative infant dose would have been less

than 0.09% of the maternal weight-adjusted dose. No adverse effects were encountered in any of the 4 infants. So, maternal azathioprine use during lactation does not appear to pose a significant immediate clinical risk to the suckling infant. Continued monitoring and long-term assessment of these infants are warranted [Moretti, 2006].

2.4.7 Methotrexate

The American Academy of Pediatrics considers methotrexate to be contraindicated during breastfeeding because of several patient problems, which include immunosuppression, neutropenia, adverse effects on growth, and carcinogenesis [Pediatrics, 1994]. So, breastfeeding during methotrexate treatment is not recommended.

2.4.8 Cyclosporine

The American Academy of Pediatrics considers cyclosporine to be contraindicated during lactation because of the potential long-term effects of immune-suppression, neutropenia, and a potential association with carcinogenesis [Pediatrics, 1994]. Breastfeeding should be discouraged in women using cyclosporine [Flecher, 1995].

2.4.9 Mycophenolate Mofetil (MMF)

There is no enough data regarding the excretion of MMF into breast milk. Lactation is not recommended while using MMF [EGRT, 2002].

2.4.10 Sulfasalazine

This is compatible with nursing. In eight mothers who were breastfeeding and taking sulfasalazine, analyses were done from mothers' serum, breast milk and serum from their children. The results showed that the amount of sulfasalazine and sulfa pyridine transferred to the child in the breast milk is negligible with regards to the risk of kernicterus [Eshjorner, 1987].

2.4.11 Tumor necrosis Factor α inhibitors (Anti-TNFα)

At present it is not known whether TNFα inhibitors are secreted into breast milk and can be ingested by mothers with breastfed child. Mothers who wish to breastfeed their children should be informed that there is insufficient knowledge to provide them with adequate information [Ostensen, 2008].

2.4.12 Rituximab

There is insufficient data to support breastfeeding in patients who are on Rituximab. So it is better to avoid Rituximab during lactation.

2.4.13 Intravenous Immunoglobulin (IVIG)

No data regarding IVIG excretion in breast milk. Therefore, we suggest avoiding breastfeeding while the patient is on IVIG.

2.5 Safety of contraception in SLE women

Premenopausal women with SLE should have access to safe and effective birth control measures. Women who have diminished fertility may seek hormonal manipulation to

stimulate ovulation, and women receiving cyclophosphamide may need methods for preserving fertility. Furthermore, exogenous estrogen may be used not only to prevent glucocorticoid-induced osteoporosis but also to treat ovarian cysts, endometriosis, irregular menses, and menorrhagia.

The high rate of elective abortion among women with SLE may reflect the failure of the birth-control method used or the absence of an adequate birth-control program [Petri, 2005; Leona, 1981]. As the disease activity during pregnancy is generally high in women who conceive, pregnancy can be particularly risky in women with active disease or on teratogenic medications. So, pregnancy should be planned to begin during period of disease quiescence making contraception an important issue for these women. All women with rheumatologic disease have contraceptive options, including barrier methods, the intrauterine device (IUDs) and oral contraceptive pills (OCPs) [Wayslett, 1991; Clowse, 2010].

Progestin-only contraceptives are not widely used because of their effects on the endometrial bleeding pattern [Mintz, 1984]. Oral contraceptives (OCPs) remain one of the most effective forms of birth control [Lauterbach, 2000]. The Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) trial of oral contraceptives versus placebo was a prospective, randomized, double blind trial that examined the effects of oral contraceptives (containing 35mg ethinyl estradiol) i.e. low estrogen dose on disease activity in 183 premenopausal women with SLE. This concluded with only 7 severe flares occurring in 91 patients receiving oral contraceptives, the same number which was recorded for the 92 women receiving placebo. To the surprise of most physicians, OCP was equivalent to placebo in terms of severe flares. So, the available data support the use of OCPs containing estrogen as birth control choice for patients with inactive or stable SLE who are at low risk of thrombosis [Petri, 2005].

The SELENA trial does not pertain to women with very active SLE, such as active lupus nephritis, or those with the lupus anticoagulant or with high titer anticardiolipin, which were excluded. OCPs cannot be prescribed to all SLE women, but when appropriate, may demonstrably improve the quality of life [Petri, 2008]. Given the high prevalence of antiphospholipid antibodies in SLE, it seems prudent not to prescribe OCPs to women with lupus anticoagulant or medium-to-high titer anticardiolipin or anti-β_2 glycoprotein [Petri, 2001]. Despite a lack of randomized studies, evidence strongly suggests that the elevated risk of thrombosis makes estrogen-containing contraceptives unsuitable for patients with APS, prior thromboembolic episodes, and severe migraine. Decisions should be individualized according to the patients' medical status, personal preference and stage of reproductive life [Sammaritano, 2007; Ashorson, 1986].

Another study evaluating the safety of OCP was conducted as a randomized, single-blinded 12-month clinical trial in women with SLE to evaluate the effects on disease activity of combined oral contraceptives, as compared to progestin-only pill and IUD. Disease activity remained mild and stable in all groups throughout the study. There were no significant differences among the groups during the trial in disease activity, incidence or probability of flares on medication use. Thromboses occurred in four patients (two in each of the two groups receiving hormones) [Sanchez, 2005].

The risk of infection associated with IUD insertion is too small to warrant routine use of prophylactic antibiotics. Recently, FDA removed immunosuppression from list of contraindications to IUD use. The use of combined oral contraceptives is possible in stable

premenopausal SLE, and who do not have any evidence of APS. Lupus patients who are APL positive or have APS should be treated with progestogens only pills (oral or Parenteral) or IUD.

2.6 Assisted reproductive therapy (ART)

Young lupus patient exposed to I.V. cyclophosphamide face the risk of premature ovarian failure. In vitro fertilization (IVF) and its associated technologies are used for infertility in patients with a wide range of etiologies, including those with SLE, and/or APS.

The first phase of ART is ovulation induction followed by in vitro fertilization (IVF) and embryo transfer (ET) in the uterus. The most threatening conditions in affected women undergoing ovarian stimulation are lupus flares and thrombosis, with the latter being especially associated with the occurrence of an overt ovarian hyper-stimulation syndrome (OHSS).

SLE manifestations in acute flares, badly controlled arterial hypertension, pulmonary hypertension, advanced renal disease, severe valvulopathy or heart disease, and major previous thrombotic events are situations in which to ARTs are to be discouraged. It is especially due to the high risk of complications in both mother and fetus during pregnancy and puerpurium. Therefore, ovarian stimulation for ovulation induction and IVF seems to be safe and successful in well-selected women with SLE and APS [Beliver, 2009].

The ovulation induction therapy (OIT) may precipitate SLE activity or APS. A careful review of the patient's history and appropriate laboratory tests should be undertaken before OIT. Clomiphene adverse effects are rare. When gonadotropins are prescribed, preventive anti-inflammatory therapy should be considered in women with SLE, in addition to heparin and/ or anti-aggregate therapy in patients with asymptomatic antiphospholipid antibodies or prior thrombotic events [Huong, 2002].

3. Pre-pregnancy counseling

Couples with SLE with or without recurrent pregnancy loss require empathy and understanding as early pregnancy loss is an emotionally traumatic experience, similar to that associated with still birth. As many patients with SLE are young women in reproductive age and some being young men, wanted to have healthy children they need to be reassured that if they follow the expert doctor's advice with careful follow-up during pregnancy, they could still have normal children. Therefore, one needs to stress the importance of preconception counseling (Table 4).

3.1 Fertility

The vast majority of patients have no problems with fertility. However occasionally some female patients may develop antibodies to ovarian tissue that interfere with development of ovum, others may have disrupted ovarian cycles which need further investigations. Infertility could be a problem in patients on long-term cyclophosphamide (more than 6 months) and its use can also cause congenital abnormalities. Therefore while the patients are on cyclophosphamide they need to be told to use reliable methods of contraception for the total duration on this drug and three months thereafter [Handa, 2006].

Preconception counseling
Assess for risk factors
Stratify high/low risk
Give realistic, evidence-based estimates for likely success and chance of problems
Discuss prematurity and handicap
Advise against pregnancy if appropriate
Make and agree prospective plan of care

Table 4. Preconception Counseling **(**Ruiz, 2008)

For pregnancies with lupus, the risk of abortion, hypertension, and embryo deformity by a therapeutic agent is higher compared to healthy pregnancies. Lupus flares can occur at any time during pregnancy, as well as several months after delivery [Clowse, 2007]. Fortunately, the majority of gravidae do not have severe SLE activity but only mild flares mainly involving skin, joints, or constitutional symptoms [Izmirly, 2010].

Not all women with SLE have the same risk of complications during pregnancy. Thus, pre-pregnancy counseling is essential to estimate the chance of both fetal and maternal mortality and morbidity (Table 4).

To reduce the risk of pregnancy it is better to have a planned pregnancy. Therefore Pregnancy is usually undertaken when

- The disease has been in remission for at least 6 months
- Who require less than equivalent of 7.5 mg of prednisone per day
- No previous renal disease, hypertension, thrombocytopenia or anti-phospholipid antibodies

High-risk patients are shown in Table 5.

An obstetrician experienced in management of high risk pregnancies is particularly desirable for women with one of these features for a better outcome of pregnancy. A previous complicated pregnancy is, by itself, an important adverse prognostic variable. Likewise, the presence of APS is closely associated with maternal thrombosis and embryo-fetal demise. Maternal anti-Ro and anti-La antibodies may cause congenital heart block in 2% of babies.

This is fortunately a rare, but very serious condition, with a high mortality rate with or without cardiomyopathy and a high chance of permanent pacemaker for majority of children with CHB [Clowse, 2007). Defining a high risk pregnancy is not absolute as it differs from patient to patient due to the presence of other confounding factors.

The testing for Anti-SSA/SSB/ U1RNP antibodies are done only in high risk population like Women with SLE, Sjogren's syndrome, Undifferentiated connective tissue disease or other connective tissue diseases, since they comprise 50-60% of NLE mothers. It is also done in mothers with previous child having neonatal lupus as the risk of neonatal lupus in next pregnancy reaches up to 25%.

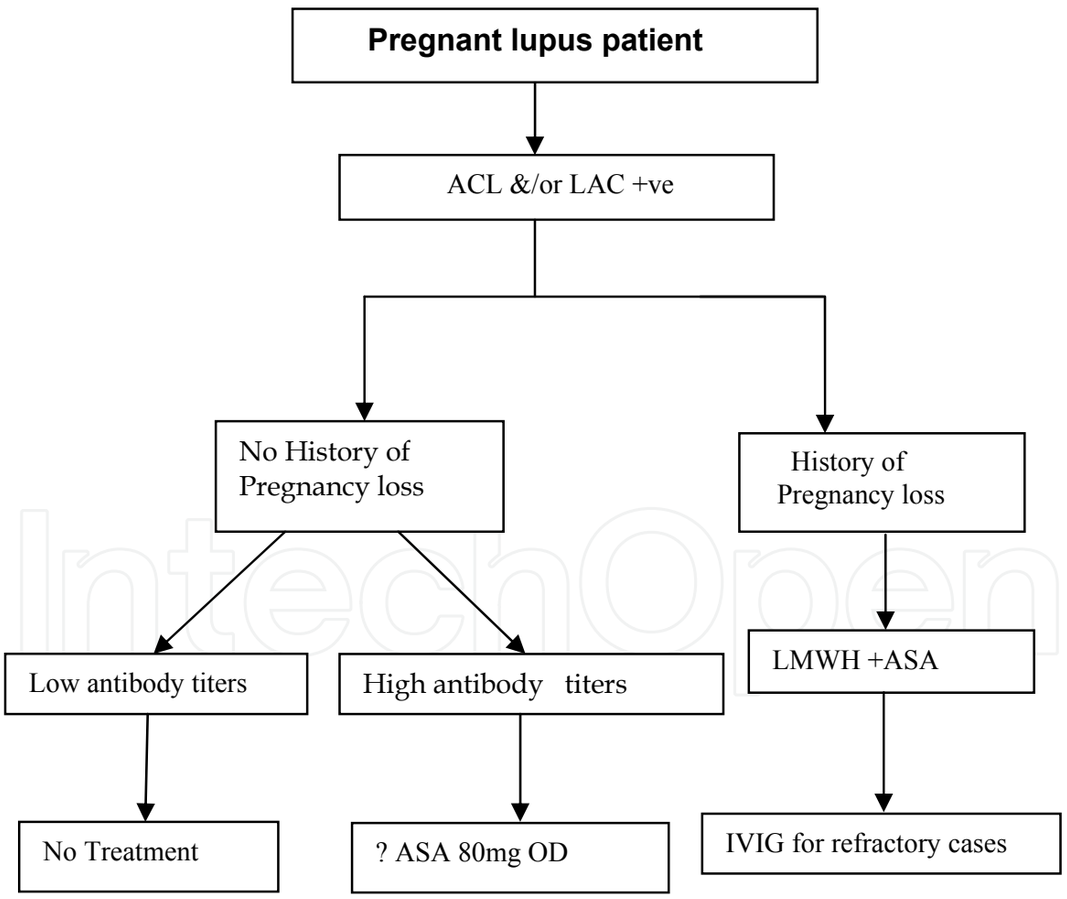
Management of a case of APS is shown in the flow chart (figure 1).

Chronic renal failure is also associated with other obstetric complications, such as hypertensive disorders and miscarriage, which are more likely to occur if renal impairment is more severe. Restrictive pulmonary disease may also worsen during pregnancy due to the thoracic compression by the growing uterus. Secondary APS is the main predictor of pregnancy complication in the form of miscarriage, fetal death, prematurity and preeclampsia. The disease activity has shown a clear association with fetal loss and

prematurity and the lupus anticoagulant confers the highest risk of miscarriages among the antibodies of APS [Handa, 2006].

High Risk Lupus Pregnancy
Previous poor obstetric history
Renal involvement
Cardiac involvement
Pulmonary hypertension
Interstitial lung disease
Active disease
High-dose steroid therapy
Other immune-suppressive therapy (cyclophosphamide, Methotrexate, etc)
Antiphospholipid antibodies/syndrome
Extractable nuclear antigens (Ro, La)
Multiple pregnancy

Table 5. High Risk Lupus Pregnancy (Ruiz, 2008)



ACL=anti-cardiolipin antibody; LAC=lupus anticoagulant

Fig. 1. Flow Chart For Management Of APS Pregnant Patient (R. Handa, 2006)

Contraindications to Pregnancy in SLE (high maternal & fetal risk)
Severe pulmonary hypertension (PAP >50 mm Hg or symptomatic)
Restrictive lung disease (FVC <1 L)
Heart failure
Chronic renal impairment with Cr >250 µmols/L
H/O severe PET or HELLP (despite ASA/LMWH)
Stroke in <6 months
Severe lupus flare in<6 months
H/O arterial thrombosis or PE

Table 6. Contraindications to pregnancy in SLE (Ruiz, 2008)

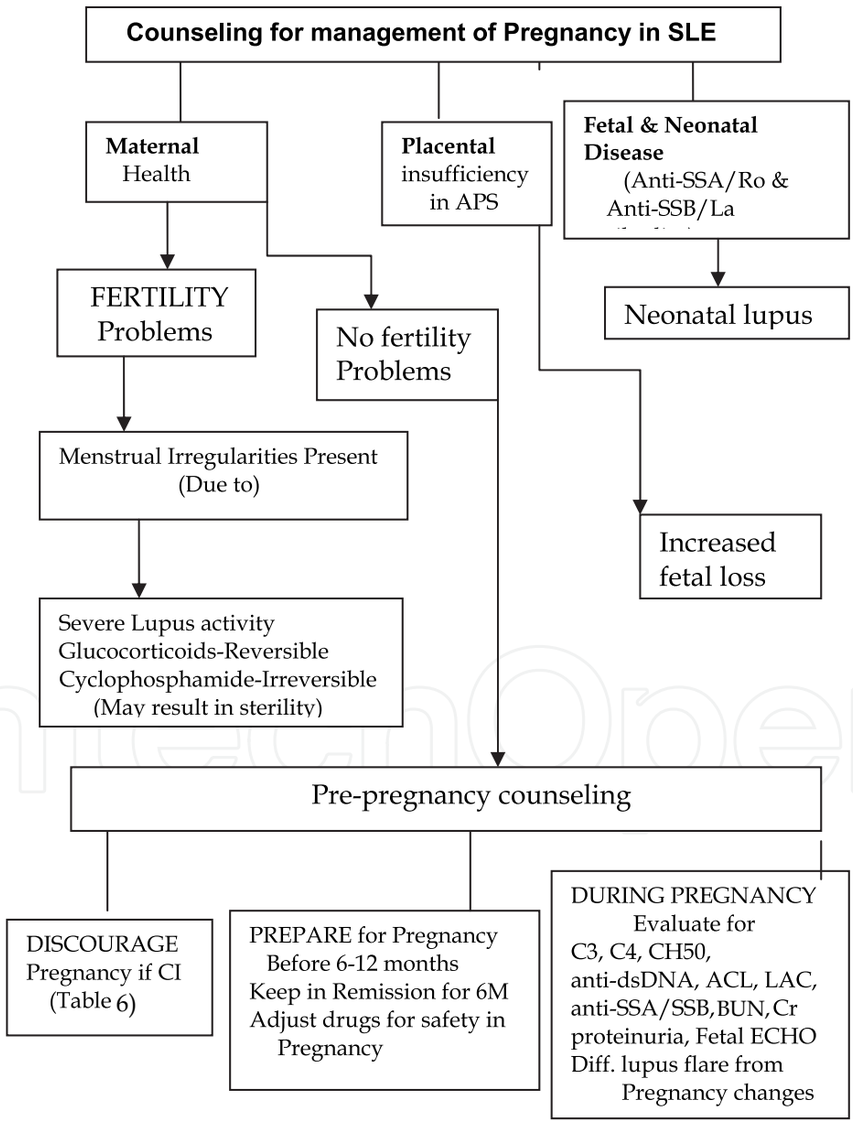


Fig. 2. Flow chart for counseling and management of pregnancy in SLE

In some extreme situations, the physicians should advise against pregnancy (Table 6). Women with current or recent lupus activity, particularly if affecting internal organs, should avoid pregnancy. The same recommendation applies to women with APS and recent thrombosis, particularly in the arterial bed. Women with severe kidney, lung or heart disease should also be discouraged from getting pregnant due to the high risk of maternal complications. Likewise, pregnancy should be considered an absolute contraindication in women with symptomatic severe pulmonary hypertension, which carries a higher than 30% maternal mortality during late pregnancy and the puerpurium.

In patients having a serum creatinine over 250 μmols/L the chance of having a successful pregnancy is <30%. Despite aggressive treatment of secondary anti-phospholipid antibody syndrome the risk of thrombo-embolism and fetal death is still high.

A major reason for discrepant results is in the definition of a lupus flare during pregnancy.

In applying the Systemic Lupus Activity Measure (SLAM) to the pregnant lupus patient, fatigue, alopecia, decreased hematocrit, and increase ESR may not represent lupus activity.

Suggestions for "valid" criteria attributable to a flare are characteristic dermatologic involvement, arthritis, hematuria, fever not secondary to infection, lymphadenopathy, leukopenia, alternative-pathway hypocomplementemia, and rising titers of antibodies to DNA. The patients with least risk in pregnancy are the patients who are in remission on < 7.5 mg of prednesalone per day, normal renal functions, no proteinuria, normal blood counts, normal BP, normal levels of complement levels and no detectable dsDNA.

The patients with moderate risk but still can be allowed to continue pregnancy with caution are-

- Patients with mild flare with arthritis, mild pleuro-pericarditis, recalcitrant skin lesions, requiring 10-15 mg of prednisalone daily for continued symptoms.
- Asymptomatic patients who have persistently elevated dsDNA and low levels of complement.

Because SLE is a progressive disease and is not curable we should not stop the couples from going for children as delaying may cause them not to have children at all. Hence, to have children earlier is better than later. Therefore one should weigh the risks and benefits and involve the patients fully in decision making.

Even platelets of 30,000-60,000, mild renal insufficiency (Cr=<200 μmols/L), proteinuria 1-2gm/day may have greater risk of flare and fetal demise but still may have successful pregnancy. Therefore such woman needs to be counseled about high likelihood of premature delivery, preeclampsia and potential need for early hospitalization for delivery [Buyon, 2004].

The minimum diagnostic work up of the couples with SLE before preconception counseling includes, detail history taking including medical, surgical, genetic, obstetrical and family history as well as thorough physical examination. Complete antibody profile needs to be done [Anti-SSA/Ro, anti-SSB/La, anti-U1 RNP antibodies, ANA, dsDNA, etc]. Anti-cardiolipin (ACL, both IgG & IgM), lupus anticoagulant (LA) are to be checked twice 6-8 weeks apart to exclude false positive results. Anti-dsDNA and complement levels to be checked every trimester, to assess the activity of the disease, along with it test for 24 hr urinary protein and serum albumin [Clowse, 2007].

Patients who are positive to anti-SSA/SSB/U1RNP needs to follow the flow chart [figure 3] for diagnosis and management of CHB which is the common presentation and has the highest mortality and morbidity in neonatal lupus [Buyon, 2004].

Screen for hypothyroidism as there is increased risk of miscarriage in subclinical hypothyroidism and incidence of hypothyroidism is found to be higher in SLE from recent studies. Test for diabetes mellitus and hyperprolactinemia and treat if present. If disease activity is present before pregnancy, the treatment needs to be started and patient should be free from disease activity at least for 6 months prior to pregnancy.

Fig. 3. Decision tree for diagnosis & management of CHB

High risk pregnancy needs a multi-disciplinary approach involving expert rheumatologist, experienced obstetrician skilled in managing high risk pregnancies, nephrologist, and neonatologist. Treatment of APS with aspirin or heparin as indicated before, during and after pregnancy.

The independent Risk Factors for pregnancy loss are Lupus activity in any trimester (but more in the first trimester), proteinuria, thrombocytopenia, hypertension in first trimester, APS and renal impairment, while the independent risk factors for pre-term delivery are increased lupus activity (before & during delivery), dose of prednisalone >7.5mg/day and hypertension [Ruiz, 2008).

Finally patients with severe active disease, high degree of end organ damage such as severe PAH, CHF, severe restrictive pulmonary disease, severe chronic renal failure are advised against becoming pregnant as they are absolute contraindications.

A significant rise in proteinuria and active sediment with or without falling complement values and rising DNA antibodies is justified to initiation the equivalent of 1 mg/kg per day of prednisalone. Moreover, the presence of proteinuria itself, even in the absence of active sediment, may warrant a trial of steroids. Persistent proteinuria > 3 grams/24 hr does not generally predict a good outcome for the mother or fetus.

In the absence of any response within two weeks, a reassessment of the situation is warranted with consideration given to the addition of cytotoxic agents and early termination, especially in the setting of deteriorating renal function and an active urinary sediment.

All patients have to practice hygienic way of living: No smoking, no alcohol, no recreational drugs, less caffeine consumption (<250mg/day) and to take folic acid supplements (at least 400 mcg/ day). All the medications prescribed needs to be checked by her attending physician and approved [Ruiz, 2011; Izmirly, 2010)].

4. Conclusion

Better outcome occurs by careful planning, patient education, close monitoring and aggressive management. All the above is important for a successful pregnancy outcome. Appropriate preconception counseling on management plans and shared care with special obstetrical & peri-natal attention will reduce the maternal and fetal morbidity and mortality.

In pregnant lupus patients the medication has to be adjusted to the patient needs depending on the disease activity, prior obstetric history, presence or absence of APS, presence of anti-SSA/Ro, SSB/La antibodies and the course of present pregnancy. So the disease manifestations, the course of pregnancy and the medications together will decide the morbidity of the mother and the child [Isenberg, 2004].

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6. References

Alan Kamada. (1994). Therapeutic controversies in treatment. *Pediatrics,*94(2): 270.

Ali, et al. (2010). Can tumor necrosis factor inhibitors be safely used in pregnancy? *Journal of Rheumatology,* 37(1): 9-17.

Ashorson et al. (1986). Systemic erythematosus, antiphospholipid antibodies, chorea, and oral contraceptives. *Arthritis Rheum*, 29(12):1535-1536

Aski LM et al. (2007). On behalf of PARIS collaborative group-antiplatelet agents for prevention of preeclampsia: a meta-analysis of individual patient data. *Lancet,* 369:1971-1980

Bar OZ, Benjamin Z, Hackman. (2001). Pregnancy outcome after Cyclosporine therapy during pregnancy: a meta-analysis 1. *Transplantation,* 71(8):1051-1055.

Baxter JD. (2000). Advances in glucocorticoid therapy. *Adv. Intern Med,* 45: 317-49.

Beliver J, Pellicer A. (2009). Ovarian stimulation for ovulation induction and in vitro fertilization in patients with systemic lupus erythematosus and antiphospholipid syndrome. *Fertil Steril,* 92(6):1803-10

Benediktsen R, Calder et al. (1997). Placenta II-β-hydroxysteroid dehydrogenase: a key regulation of fetal glucocorticoid exposure. *Clinical Endocrinology*, 46(2): 161-166.

Bonnie L, Bermas MD. (1995, Dec). Effects of immunosuppressive drugs during pregnancy. Dec; 38(12): 1722-1732

Boumpas DT, Austin HA, Fessler et al. (1995). Systemic lupus erythematosus: emerging concept, part 2: dermatologic and joint disease, the antiphospholipid antibody syndrome, pregnancy and hormone, morbidity and mortality, and pathogenesis. *Ann Intern Med*, 123(1): 42-53.

Briggs GG, Freeman RK, Yaffe SJ. (2005). *Drugs in pregnancy and lactation*. 7th ed. Philadelphia (PA): Lippincott Williams & Wilkins. 136-139.

Buyon et al. (2004). Management of SLE during pregnancy: A decision tree. *Rheumatologia*, 20 (4), 197-99

Carmona F, Font J, Cervera R et al. (1999). Obstetrical outcome of pregnancy in patients with systemic Lupus erythematosus: a study of 60 cases. *Eur J Obstet Gynecol Reprod Biol*, 83:137-42..

Chakra Varty. (2011). Pregnancy outcomes after maternal exposure to rituximab. *Blood,* 17(5):1499-506Clowse ME et al. (2005). Cyclophosphamide for lupus during pregnancy. *Lupus,* 14(8): 593-7.

Clark Ca et al. (2003).Preterm deliveries in women with systemic lupus erythematosus. *J Rheumatol,* 30:2127-32.

(2005).Decrease in pregnancy loss rates in patients with systemic lupus erythematosus over a 40-year period. *J Rheumatol*, 32:1709-12.

Clowse ME et al. (2004). Complement and doublestranded DNA antibodies predict pregnancy outcomes in lupus patients. *Arthritis Rheum*, 50:S408.

(2005). The impact of increased lupus activity on obstetric outcomes. *Arthritis Rheum,* 52(2); 514-521.

(2007) Lupus activity in pregnancy. *Rheum Dis Clin North Am*, 33:237-52.

(2008). A national study of the complications of lupus in pregnancy. *Am J Obstet Gynecol,* 199:127.e1-6.

Costedoat-Chalumeau N, et al. (2005). Safety of hydroxychloroquine use in pregnant patients with connective tissue diseases. *Autoimmune Rev*, 4(2):111-5.

Committee on Drugs, American Academy of Pediatrics. (1994). The transfer of drugs and other chemicals into human milk. *Pediatrics*, 93: 137-150.

Cooper WO et al. (2006). Major congenital malformations after first trimester exposure to ACE inhibitors. *New English Journal of Medicine*, 354(23):2443-5

Crowley P. (2000). Prophylactic corticosteroids for pre-term delivery. *Cochrane Database Syst. Rev*, 2: CD 000065.

Da Boer NK, Jarbandhan SV, de Gra FP. (2006). Azathioprine use during pregnancy: unexpected intrauterine exposure to metabolites. *Amj Gastroenerology,* 101(6): 1390-2.

Doria A, Tincani and M.Lockshin. (2008). Challenges of lupus pregnancy. *Rheumatology (Oxford),* March 47 Suppl.3.iii 9-12.

En Hams. (2002). Antirheumatic drugs in pregnancy. *Lupus*, 10(11): 683-689.

Erickson RW, et al. (1994). Treatment of hemorrhagic lupus pneumonitis with plasmaphresis. *Semin Arthritis Rheum*, 24: 114-123.

Eshjorner E, Jarnerot et al. (1987). Sulphasalazine and sulphapyridine serum levels in children to mothers treated with sulphasalazine during pregnancy and lactation. *Acta Paediatric Scand*, 76(1): 137

European best practice guidelines for review transplantation. (2002)

Section IV: long-term management of the transplant recipient. IV-IOS Pregnancy in renal transplant recipients. *Nephrol Dial Transplant,* 17 (Suppl. 4): 50-55.

Flecher SM, Katz AR, Rogers AJ. (1985). The presence of cyclosporine in body tissues and fluids during pregnancy. *American Kidney,* 5(1): 60-3.

Francis L. Pharmacotherapy of systemic lupus erythematosus. (2009). *Expert Opin Pharmacother,* 10(9): 148-94.

Fox R. (1996). Antimalarial drugs: possible mechanisms of action in autoimmune disease and prospects for drug development. *Lupus,* 5(supp.): S4-S10.

Gladman DD, Urowitz MB, Senecal JL, *et al*. (1998). Aspects of use of antimalarials in systemic lupus erythematosus. *Journal of Rheumatology*, 25(5): 983-985.

Guillermo Riuz-Irastorza et al. (2009). Managing lupus patients during pregnancy. Best practice & research, clinical rheumatology, 23:575-582

Guinn DA, Atkinson MW, Sullivan et al. Weekly courses of antenatal corticosteroids for women at risk of preterm delivery: a randomized controlled trial. *JAMA,* 286(13): 1581-7.

Hawkins, et al. (1997). Anesthesia-related death during obstetric delivery in the United States,1979-1990. *Anesthesiology*, 86: 277-284.

Horlocker TT, Bajwa ZH, Ashraf et al. (2002). Risk assessment of hemorrhagic complications associated with non-steroidal anti-inflammatory medications in ambulatory pain clinic patients undergoing epidural steroid injection. *Anesth Analg,* 95(6): 1691-7.

Howard CR, Lawrence RA. (1994). Drugs and breastfeeding. *Clinical Perinatology*, 26: 447-78.

Huong DL, et al. (2001). Pregnancy in the past or present lupus nephritis: a study of 32 pregnancies from a single center. *Ann Rheum Dis,* 60(6): 599-604.

(2002). Importance of planning ovulation induction therapy in systemic lupus erythematosus and antiphospholipid syndrome: a single center retrospective study of 21 cases and 114 cycles. *Semin Arthritis Rheum*, 32(3): 174-88

Isenberg DA et al. (2004). Pregnacy in rheumatic disease- an overview. *Oxford text book of Rheumatology*, 2004, 3rd edition, p 117-125

Janssen NM, Genta M. (2000). The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy and lactation. *Arch Intern,* 160: 610-619.

Jick H, et al. (1981). First trimester drug use and congenital disorders. *JAMA*, 246: 343-346.

John Fredrick. (2000). Pregnancy complications and delivery practice in women with connective tissue disease and inflammatory rheumatic disease in Norway. *AOGS* 79(6):490-495.

Karim MY, Alba P *et al*. (2002). Mycophenolate mofetil for systemic lupus Erythematosus refractory to alter immunosuppressive agents. *Rheumatology (Oxford)*, 41: 876-882.

Kiss E, Bhattoa et al. (2002). Pregnancy in women with systemic lupus erythematosus. *European Journal of Obstetric Gynecology Reproductive Biology* 2002; 101(2): 129-34.

Koblayash et al. Immunosorbent plasmapheresis for a patient with antiphospholipid antibody syndrome during pregnancy. *Ann Rheum dis*, 51:399-401.

Kozer E et al. (2003). Effects of aspirin consumption during pregnancy on pregnancy outcomes: meta-analysis. *Birth defects Res B Dev Reprod Toxicol*, 68(1):70-84

Lee BH, Stoll BJ, McDonald SA, Higgins RD. (2008). Neurodevelopmental outcomes of extremely low birth weight infants exposed prenatally to dexamethasone versus betamethasone. *Pediatrics*, 121(2): 1503-1510.

Lauterbach GL, et al. (2000). Women's health. *Rheum Dis Clinics NAM*, 25: 539-566.

Leona, et al. (1981). Systemic lupus erythematosus in pregnancy. *Ann Intern Med*, 94(5): 667-77.

Levy RA et al, (2001). Hydrozychloroquin in lupus pregnancy: Double blind and placebo controlled study. *Lupus*, 10(6):401-404

Lewis R, Laversen NH, Birnbaum S. (1972). Malaria associated with pregnancy. *Obstetric Gynecology*, 42: 696-700

Magee LA, Sibai B. (2011). How to manage hypertension in pregnancy effectively *British Clinical Pharmacology*, 10,111/j: 1365-2125.

Mintz, et al. (1984). Contraception with progestogens in systemic lupus erythematosus. *Contraception*, 30: 29-38.

Mpetvi. (1996). Hydroxychloroquine use in the Baltimore lupus cohort: effects on lipids, glucose and thrombosis. *Lupus*, (5): supp.1.

National Institutes of Health Report of the Consensus Development Conference. *(1994). On the effect of corticosteroids for fetal maturation on perinatal outcome. NIH publication no. 95-3784*.

Notion RL, Hackett LP, Dusci LJ, IIett KF. (1984). Excretion of hydroxychloroquine in human milk. *British Journal of Clinical Pharmacology*, 17(3): 368-9.

Ostensen, ME etal. (1985). Hydroxychloroquine in human breast milk. *European Journal on Clinical Pharmacology*, 28(3): 357.

(1994). Optimisation of antirheumatic drug treatment in pregnancy. *Clinical Pharmacokinetics*, 27(6): 486-503.

(1996). Safety of non-steroidal anti-inflammatory drugs during pregnancy and lactation. *Inflammopharmacology,* 24(3), 4(1): 31-41.

(2006). Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res Ther,* 8: 209-218

(2008). Update on safety during pregnancy of biological agents and some immunosuppressive anti-rheumatic drugs. *Rheumatology (Oxford),* 47 suppl.3: iii 28-31.

(2011). Treatment with biologics of pregnant patients with rheumatic diseases. *Curr Op in Rheumatology,* 23(3): 293-8.

Perricone R, C. De Carolis. (2008). Intravenous immunoglobin therapy in pregnant patients affected with systemic lupus erythematosus and recurrent spontaneous abortion.*Rheumatology (Oxford)*, 47(5): 646-651.

Petri M et al. (2001). Exogenous estrogen in systemic lupus erythematosus: oral contraceptives and hormone replacement therapy. *Lupus,* 10: 222- 226.

(2005). Combined oral contraceptives in women with systemic lupus erythematosus. *N Engl J Med*. 353: 2550-2558.

(2008). Editorial: oral contraceptives in systemic lupus erythematosus: the case for (and against). *Lupus*, 17: 708-710.

Rawetz. (2004). Anesthesiological aspects of pregnancy in patients with rheumatic disease. *Lupus,* 13: 699-702.

Raybum WF. (1992). Glucocorticoid therapy for rheumatic disease: maternal, fetal and breastfeeding considerations. *American Journal of Reproductive Immunology*, 28(3-4): 138-40.

Rahman P, Gladman DD, Urowitz MB. (1998). Clinical predictors of fetal outcome in systemic lupus erythematosus. J Rheumatol, 25:1526-30.

Ruiz et al. (2004). Evaluation of systemic lupus erythematosus activity during pregnancy. *Lupus,* 13:679-82.

Sammaritano LR. (2007). Therapy insight: guidelines for selection of contraception in women with rheumatic diseases. *N Clin Pract Rheumatol*, 3(5): 273-81.

Sanchez-Guerrero J, et al. (2005). A trial of contraceptive methods in women with systemic lupus erythematosus. *N Engl J Med*, 353: 2539-2549.

Simister NE. (2003). Placental transplant of immunoglobulin G. *Vaccine,* 21(24): 3365-9.

Sperber K, Hom C, Chao et al. (2009). Systemic review of Hydroxychloroquine use in pregnant Patients with autoimmune diseases. *Pediatric Rheumatology Online J,* 7: 9.

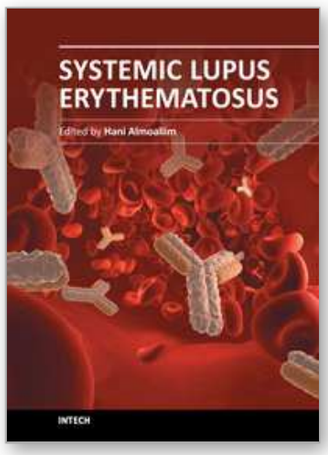
The American Academy of Pediatrics and the American College of Obstetricians and Gynecologist. (2002). *Antepartum Care. In: Guidelines for perinatal care, 5th edition*: Washington DC:73-127.

Vonderleij S, et al. (1994). Successful outcome of pregnancy after treatment of maternal anti-Ro (SSA) antibodies with immunosuppressive therapy and plasmapheresis. *Prenat Diagr* 14: 1003-1007

Wallance DJ, et al. (2001). Apheresis for lupus erythematosus: state of the art. *Lupus,* 10:193-196.

Wiernik PH, Duncan JH. (1971). Cyclophosphamide in human milk. *Lancet*, 1(7705): 912-914.

Yasmeen S, et al. (2001). Pregnancy outcomes in women with systemic lupus erythematosus. *J Matern Fetal Med,* 10: 91-6.



Systemic Lupus Erythematosus

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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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