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NEWSLETTER

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CONTENTS

NEWSLETTER Obstetric Medicine

From the Editor's Desk

Dear SOMI Members,

Rheumatological diseases often occur in young women in whom pregnancy is an expected event. In the past, pregnancy was considered dangerous in women with autoimmune diseases. With appropriate pre-pregnancy counselling, controlling disease activity before planning pregnancy, modifying drugs which are more suitable for pregnancy, pregnancy outcomes have improved to a great extent. Pregnancy may affect the course of an autoimmune disease. Rheumatoid arthritis tends to improve during pregnancy and there may be postpartum flare-ups. Antiphospholipid antibody syndrome (APLA) usually gets worse during pregnancy. SLE may flare up in a third of patients in pregnancy. Rheumatological diseases affect outcomes of pregnancy. SLE is associated with increased risk of preeclampsia and APLA with recurrent pregnancy losses. Effect of disease on the pregnancy and effect of pregnancy on the disease varies from one connective tissue disease to another!

This edition of e-newsletter covers SLE and fetal outcomes, APLA and drugs commonly used in management of autoimmune diseases and their safety in pregnancy and lactation. I thank all the authors for their contribution and request all members to contribute to our next issue. Our next issue will be focusing on neurological disease in pregnancy. Please send in your articles (case reports, original research or review articles) to obsmedindia@gmail.com with cc to drharikishan@gmail.com. Please contact me for any further clarifications.

Yours sincerely,

Dr. Hari Kishan Boorugu
Editor

NEWSLETTER Obstetric Medicine

Antiphospholipid Syndrome in Pregnancy

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Introduction

Antiphospholipid Antibody syndrome (APS) also known as Hughes' syndrome is a hypercoagulable multisystem disorder with or without pregnancy morbidity in the presence of persistent antiphospholipid antibodies (aPL). aPLs are a heterogenous group of antibodies directed against phospholipid-binding proteins. APS can occur as a primary condition or secondary to an autoimmune disease. Catastrophic APS (CAPS) is a rapidly progressive thromboembolic disease involving simultaneously three or more organs, organ systems or tissue leading to functional defects.

Incidence

In patients without an underlying autoimmune disorder, the association between aPL and pregnancy loss was 9%, stroke 14%, myocardial infarction 11% and deep vein thrombosis 10% as reported by APS Action, an international research network. aPL occurs in 1-5% of general population, 30-40% of women with SLE and 6-15% with other autoimmune connective tissue disorders. 30% of women with severe early onset Preeclampsia have aPL. Thrombotic events occur in 30% of those with aPL.

Pathogenesis

Beta2 Glycoprotein I (Beta2GPI), a cofactor which enables the binding of aCL to cardiolipin plays a major role in the thrombotic events associated with APS. In those who suffer a fetal loss there is placental infarction and thrombosis of decidual vessels. Apart from this there is activation of complement cascade and inflammatory processes which play a role in the pathogenesis.

Clinical manifestations

APS presents with protean manifestations involving multiple organs, of which thrombotic events and pregnancy morbidities form the diagnostic criteria.

Disease defining Clinical manifestations of APS

Thrombosis :
This is the hallmark of APS, venous being commoner than arterial. It occurs in 20-30% of patients and can involve unusual sites. Superficial thrombophlebitis is not uncommon.

Arterial thrombosis is most common in cerebral vasculature, which presents as stroke (20%) and TIA (11%). Small vessel involvement as in thrombotic microangiopathy in kidney, occlusion of retinal, coronary and mesenteric arteries can also occur.

Pregnancy morbidities
This includes early fetal loss, 3 or more consecutive miscarriages (<10 weeks gestation), unexplained by chromosomal defects or by maternal anatomic or hormonal causes, one or more fetal death (>10 weeks of gestation with normal fetal morphology), one or more premature birth (<34 weeks gestation due to preeclampsia or severe placental insuffiency.)

Other clinical manifestations of APS

Neurological manifestations
Migraine, epilepsy, chorea, tranverse myelitis, cerebellar ataxia.

Hematologic abnormalities
Thrombocytopenia, autoimmune hemolytic anemia.

Cardiac manifestations
Valvular thickening, Libman-sacks vegetations especially of the mitral valve, hypertension, pulmonary hypertension and coronary artery disease.

Cutaneous manifestations
Leg ulcers, Lividoreticularis (Livido reticularis in association with stroke is called Sneddon syndrome and this occurs in the presence of aPL).

Pulmonary manifestations
Thromboembolic and nonthromboembolic pulmonary hypertension, Pulmonary arterial thrombosis, ARDS and diffuse alveolar hemorrhage.

Adrenal disease
Hypocorticolism due to adrenal vein thrombosis and hemorrhagic infarction.

Arthalgias, arthritis, involvement of gastrointestinal system, kidneys and eyes.

Catastrophic APS (CAPS)
Multiorgan system failure arising due to diffuse thrombotic disease in a subset of patients is called CAPS which commonly involve small blood vessels in various organs. Discontinuing treatment, trauma, surgery and infections can be CAPS triggers.

NEWSLETTER Obstetric Medicine

Antiphospholipid Syndrome in Pregnancy

Classification criteria for CAPS: Table1

Criteria	Classification	Probable CAPS
1. Evidence of involvement of three or more organs, systems and /or tissues 2. Development of symptoms simultaneously or in less than a week 3. Confirmation by histopathology of small vessels occlusion in at least one organ tissue 4. Laboratory confirmation of aPL antibodies	Definite CAPS ▪ Requires all four criteria	▪ All 4 criteria, except for only two organs, systems and/or sites of tissue involvement or ▪ All 4 criteria, except for lab confirmation 6 weeks apart due to the early death of a patient never tested for aPL before CAPS or ▪ Criteria 1, 2 and 4 above or 1, 3 and 4 and the development of a third event in more than a week but less than a month despite anticoagulation.

Primary APS and APS with SLE

Though the clinical manifestations of both conditions are similar, distinction is important and those with primary APS should not be diagnosed as having lupus. Primary APS is less likely to be associated with systemic manifestations, thrombosis and pregnancy morbidities than APS associated with SLE. APS can evolve into SLE in some patients as years progress.

Post partum syndrome

This is a rare syndrome characterized by pleuro-pulmonary disease, fever and cardiac manifestations.

Laboratory findings and diagnosis of APS

This involves testing for aPL antibodies:

- aCL; IgG and/ or IgM by ELISA
- Anti-beta2-GPI antibodies; IgG and/or IgM by ELISA
- Lupus anticoagulant testing

The association of IgA and thrombosis is not well established. According to the Laboratory diagnostics and trends, APS task force of the 14th International congress on aPL , the quality of evidence to test for IgA is low though Systemic Lupus international collaborating clinics include IgA and anti Beta2- GPI as definition criteria.

Testing for aPL is performed at the time of thrombosis or pregnancy morbity. But in the presence of a large thrombus or anticoagulants, the results of aPTT or LAC may be erroneus though ELISA assays for aCL or beta-2 GP I are not affected. If tests are initially positive, they should be confirmed after twelve weeks. If initial tests are negative, additional antibodies testing is not required unless clinical suspicion is very strong.

Clinically significant aPL is defined as one or more positive aPLs on two or more occasions twelve weeks apart.

- Positive LAC test.
- ACL IgG or IgM in a titre of >40 units.
- Anti-beta2-GP I IgG or IgM in a titre of >40 units.

Diagnosis of APS is based on a combination of clinical features and Lab findings. Though there are limitations to this in the clinical setting, this is of use in diagnosing the condition.

Lupus anticoagulant

This is the most relevant assay in relation to vascular events and obstetric morbidity. LAC is a misnomer because it prolongs coagulation time in vitro. The presence of LAC may be indicated by prolonged aptt or false positive RPR test for syphilis. Abnormalities of these tests should warrant further evaluation. In patients with LAC, aptt will not become normal when mixed with normal plasma in 1:1 proportion, whereas it would normalize in those with factor deficiency. It corrects with excess phopholipid. It can also be detected by direct anti-Xa assay such as the dilute Russel viper venom assay (dRVVT). As the LAC activity is heterogenous, it is recommended that at least two methods are performed.

Other laboratory findings include thrombocytopenia and proteinuria secondary to renal vasculopathy.

NEWSLETTER Obstetric Medicine

Antiphospholipid Syndrome in Pregnancy

APS Classification criteria: Table2

Clinical Criteria	Pregnancy morbidity
Vascular thrombosis One or more episodes with unequivocal imaging or histological evidence of thrombosis excluding superficial venous thrombosis.	**Laboratory criteria** The presence of one or more of the aPL on two or more occasions at least 12 weeks apart. ▪ aCL IgG and/ or IgM by ELISA. ▪ anti-beta GP I IgG and/or IgM by ELISA. ▪ LAC activity according to published guidelines.

APS is present in patients who meet at least one clinical and one laboratory criteria according to the revised Sapporo APS classification also known as the Sydney criteria.

In patients who do not meet the criteria but the index of suspicion is high like unexplained thrombocytopenia, valvular heart disease, aPL nephropathy and aPL related clinical events with borderline lab values, the opinion of a clinician with expertise in APS should be sought.

Pregnacy and APS

Effect of pregnancy on APS

Pregnancy increases the risk of thrombosis in APS. If there had been a previous history of venous thrombosis, the risk for venous thrombosis is increased in pregnancy and it is similar for arterial thrombosis. Thrombocytopenia may get worse.

Effect of APS on pregnancy

Pregnancy morbidities as discussed earlier are increased. FGR and oligohydramnios preceed fetal death. In those with aPL and SLE the pregnancy loss is independent of lupus. Adverse outcome is higher in those with LA, which was present in 69% of patients in the PROMISSE study. High titres of IgG aCL could also be a marker. However previous obstetric history is the best predictor of pregnancy outcome. Preeclampsia is severe and of early onset.

Neonatal APS

The diagnostic criteria for Neonatal APS is the same as the rest of the population though the presence of aPL could be because of placental transfer, which disappears in six to twelve months, if it is due to passive transfer.

Management

Pre-pregnancy

Women with history of clinical feature suggestive of APS or pregnancy morbidities as mentioned in diagnostic criteria should be screened for LA and aCL. A detailed history to exclude other causes of fetal loss like cervical incompetence is important because diagnosis cannot be made only based on positive aPL.

Prepregnancy planning

1) Review medical and obstetric history
2) Lab assessment for antibodies, thrombocytopenia, anemia testing for anto-Ro, and La antibodies may be helpful even when there is no evidence of SLE because of the association of these antibodies with 2% risk of complete heart block in the fetus and 5% risk of neonatal lupus.
3) Pre-pregnancy treatment : Assess general health, review of drug therapy. Postpone pregnancy if recent thrombotic event or active SLE is present.

Treatment of pregnant women with APS

Management of pregnant women with APS should be by a multidisciplinary team with expertise in this condition. Those with aPL but no clinical features will be benefited by Aspirin. Those with history of thrombosis will require anticoagulants. If recurrent miscarriage is the presenting feature, aspirin alone or aspirin and Low molecular weight heparin (LMWH-Enoxparin 40 mg) or Unfractionated heparin (UFH) 5000IU sc may be appropriate. Heparin is associated with osteoporosis in 1-2% of women. Supplementation with 1500 mg/day of calcium is recommended.

It is important to carry out a close fetal monitoring.

Uterine artery Doppler waveform analysis at 24-28 weeks, monthly growth scans from 28 weeks if pre-diastolic notching or a high resistance index is present in the uterine artery, Doppler waveform and surveillance for early onset preeclampsia will all improve the fetal outcome.

Peripartum management

LMWH is to be replaced with unfractionated heparin at 36 weeks and this can be discontinued at the onset of labour or 24 hours before planned induction or section. Women with prior history of thrombosis should not discontinue anticoagulants for more than 48 hours. Though aspirin may be discontinued after 36 weeks, in those with history of stroke the benefit of continuing it outweighs the risk of minor surgical bleeding.

NEWSLETTER Obstetric Medicine

In women with treatment failure resulting in therapies like IVIG, therapeutic plasma exchange, glucocorticoids and other cytotoxic drugs have not been proven to be very useful. Miscarriage rates have been similar in those prescribed hydroxychloroquine.

In women with CAPS, any trigger if present should be treated. Heparin should be started and if there is no recurrent thrombi or bleeding it can be replaced by oral anticoagulants. High dose methylprednisolone (1gmIV for 3 days) followed by Prednisolone (1mg/kg) should be administered. Plasma exchange for five days with or without IVIG (400MG/kg/day) has been found to improve survival. In patients who are resistant to standard therapy, treatment with Rituximab, Eculiximab may be helpful.

Contraception

Women with aPL should avoid estrogen containing oral contraceptives.

Summary of treatment of pregnant women with APS: Table 3

Clinical History	Antepartum treatment	Postpartum treatment
No thrombosis, miscarriage, adverse pregnancy outcome	Aspirin 75 mg from preconception	Postpartum thromboprophylaxis according to other risk factors
With prior history of thrombosis	If on Warfarin/Acitrom switch over to aspirin and enoxparin 40mg b.d as soon as pregnancy is confirmed If not on oral anticoagulants, aspirin 75 mg preconception, enoxparin 40 mg o.d once pregnancy is confirmed and b.d at 16-20 weeks	On long term Warfarin/Acitrom, recommence after 5-7 days, discontinue LMWH once INR >2 Otherwise LMWH for 6 weeks
Recurrent miscarriage <10 weeks	Not on prior treatment: Aspirin 75 mg o.d from preconception Prior miscarriage with aspirin: Aspirin 75 mg preconception. Enoxparin 40 mg o.d once pregnancy is confirmed, can be discontinued at 12 or 20 weeks of gestation if uterine artery waveform is normal.	
Late fetal loss, adverse outcome due to preeclampsia, abruption, FGR	Preconception ; 75 mg Aspirin od Enoxparin 40 mg o.d once pregnancy confirmed	LMWH 10 days to 6 weeks depending on presence of other risk factors

Source: 'Hand book of Obstetric Medicine' by Catherine Neelson Piercy

Prognosis

With proper evaluation, pre-pregnancy counseling and monitoring during antenatal period, favourable outcome can be achieved in 80% of pregnancies. According to the European Registry of Obstetric APS, the maternal fetal outcome in obstetric APS is very good compared to classical APS. Recurrent thrombotic events can be prevented with careful management of anticoagulation. Some patients with APS may develop SLE.

Conclusion

APS is a syndrome defined by clinical and laboratory criteria. Treatment should be by a multidisciplinary team with expertise in managing this condition. Inspite of problems of heterogenisity associated with it and lack of consensus on treatment, the outcome for pregnant women with disorder has considerably improved over the last few years.

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NEWSLETTER Obstetric Medicine

Fetal Complications in Systemic Lupus Erythematosus

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Introduction

Systemic lupus erythematosus (SLE), Rheumatoid arthritis and Sjogren's syndrome are the common autoimmune conditions. 2 /1000 women are affected with these conditions during their lifetime, predominantly in the childbearing age. The diagnostic criteria for SLE was validated by the Systemic Lupus International Collaborating Clinics group[1]. The 2004 Sapporo classification criteria is used to confirm antiphospholipid antibody syndrome (APS)[2].

Fetal complications associated with SLE

Women with SLE have a 2 to 4-fold increased rate of pregnancy complications. Prematurity, small for gestational age (SGA), miscarriage, intrauterine death are the common fetal complications. Fetal loss occurs on an average in 20 - 30% of pregnancies. Except from anomalies and heart block, there is no significant increase in neonatal mortality rate.

The congenital anomaly risk is increased to 2-7% compared with 2-3% in uncomplicated pregnancies, commonly from congenital heart disease. Sjogren's syndrome, APS and use of certain drugs like ACE inhibitors increases the anomaly risk.

Congenital heart block (CHB) can occur due to autoimmune disorders, familial inheritance or cardiac anomalies. In autoimmune disorders, SSA (Ro) or SSB (La) antibodies and rarely ANA cause CHB. It occurs in ~1–2% of Ro-positive women with recurrence risk 10 times higher in the subsequent pregnancies. In a large series of 214 high degree heart block and a 7 year follow-up, 79% required a pacemaker, 19% developed dilated cardiomyopathy and 12% died[3].

Fetal growth restriction (FGR) was observed in 14-33% and preterm births in 10-28%. Unrecognized autoimmune disorders can be identified for the first time after a pregnancy complication and can be responsible for up to 25 % of FGR and up to 34 % of preeclampsia[4]. Fetal complications have vastly improved from 44% to 17% over the last four decades. Table 1 lists the fetal outcome in SLE from the recent Cochrane review consisting of 11 studies with a total number of 529,778 participants[5].

Pathophysiology

Animal models show that complement activation plays a pivotal role in SLE pregnancy morbidity, but the exact pathways in humans are insufficiently understood. In humans, diffuse C4d staining at the feto-maternal interface was present, almost exclusively in patients with intrauterine fetal death ($p = 0.03$)[8].

There are several possible mechanisms hypothesised for antiphospholipid antibodies to cause a pregnancy complication. APL crosses the placenta. It activates endothelial cells to express adhesion molecules6 and activates platelets to induce a pro-coagulant state[7].

Cytokines, such as transforming growth factor beta (TGF-β) are substantially lower and causes CHB by focal cellular death during active cardiac remodeling, within an already formed cardiac septation[6].

Predictors of fetal complications

Coexisting antiphospholipid antibody syndrome, Sjogren's syndrome, pre-pregnancy anti dsDNA activity, cyclophosphamide, steroids use, renal (past or present), haematological involvement (especially thrombocytopenia9), hypertension, active lupus at conception and flares during pregnancy are associated with an unfavourable fetal outcome. In some studies, previous lupus nephritis only had a higher rate of maternal complications and was not associated with increased fetal risks[10].

Arthritis, serositis[11], current hydroxychloroquine therapy and presence of anti-prolactin (PRL) antibody are associated with a favourable fetal outcome.

Pregnancy management: Maternal evaluation

Uncomplicated SLE in remission is associated with a good overall prognosis. Frequent antenatal reviews are required with, at the most, fortnightly gaps. Clinical assessment for signs of flares, organ involvement, edema, blood pressure, proteinuria and clinical abdominal palpation (from 26 weeks) should be undertaken at every antenatal visit. Identification of disease severity and exacerbations are vital.

Pregnancy Disease Activity Index (SLEDAI), systemic lupus activity measure scale (SLAM), British Isles Lupus Assessment Group (BILAG) index, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index, European Consensus Lupus Activity Measurement (ECLAM) are different disease severity indices that can be used in clinical care[12].

The comprehensive list of investigations in SLE evaluation is listed in table 2. The prime purpose is to rule out co-existing APS, Sjogren's Syndrome and assess disease severity. Investigations should be individualised as the entire panel is neither cost-effective nor necessary for all SLE pregnancies.

Anaemia and thrombocytopenia are common due to lupus-related immune haemolytic anaemia. Low complement levels are generally associated with increased SLE activity. But during pregnancy, C3 and C4 may rise to above normal levels, and thus a flare with complement activation may occur despite apparently normal levels of C3 and C4. If C3 or C4 levels drop by more than 25%, it may indicate disease activity. Studies are contradictory about C3 or C4 as predictors of overall disease activity in pregnancy[13].

Pregnancy management: Fetal evaluation

Accurate gestation assessment in 1st or early 2nd trimester should be performed by ultrasound scan. Fortnightly viability confirmation is required until patient has perception of fetal movements.

Serial ultrasound examination for fetal heart rate is required in SSA/SSB positive and past CHB. Ideally every 5-7 days, fetal heart rate and PR interval should be recorded between the 18th and 28th weeks. Using the gated-pulsed Doppler technique, time intervals from the onset of the mitral A wave (atrial systole) to the onset of the aortic pulsed Doppler tracing (ventricular systole) within the same left ventricular cardiac cycle may be measured. This time interval represents the mechanical PR interval[14].

Uterine artery doppler pulsatility index (PI) and diastolic notch at 20 - 24 weeks are useful in predicting placental dysfunction. Biochemical tests like low PAPP-A (9-13 weeks), high alpha feto protein (16-19 weeks) and low placental insulin like growth factor are additional serum markers for placental insufficiency. In SLE, even with normal uterine artery doppler and biochemical markers, placental insufficiency risk is moderately increased (~LR 10), whereas presence of abnormal average PI significantly increases the pregnancy risk (>LR 15).

Assessment of fetal growth is required serially from 24-26 weeks. Fetal Doppler studies (umbilical, middle cerebral artery Doppler and ductus venosus) are helpful in timing of delivery in fetal growth restriction (FGR). Doppler signs of fetal decompensation warrants delivery even if preterm gestation. Beyond 36 weeks, there should be a low threshold for delivery in FGR, as sudden fetal deterioration can occur and doppler only has limited value in predicting such complications.

Role of SLE medications on fetal outcome

Low dose aspirin (oral dose 75mg) has an established safety profile in pregnancy and is indicated in SLE to reduce placental insufficiency from early pregnancy until 36 weeks of gestation. The use of aspirin and prophylactic dose of low molecular weight heparin improves outcome in APS. But 20-30% may still develop a complication. In such situations, experts suggest adding HCQ may of benefit, particularly if past thrombosis or ischaemic placenta-mediated complications. Further studies are required to evaluate HCQ and confirm the clinical benefit of this hypothesis. At 37 weeks, elective delivery is advised. To reduce the risk of postpartum deep vein thrombosis, antithrombotic coverage of the post-partum period is recommended in all SLE women, with or without previous thrombosis.

Betamethasone in first degree CHB helps to prevent its progression. The use of fluorinated steroids was neither associated with survival nor with regression of 2nd degree CHB3. High grade CHB requires long term cardiology follow-up and during pregnancy may benefit from plasmapheresis and IV immunoglobulins[15].

Antihypertensive drugs are frequently needed in pregnant women with SLE but angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, diuretics are contraindicated. This is due to the fetal toxicity on the kidneys, renal failure, oligohydramnios,

fetal anomalies (ACE inhibitor fetopathy), neonatal arterial hypotension and death have been reported. Those on antihypertensive agents need to be converted to drugs suitable for pregnancy.

In a study on prescribing trends with immunomodulatory agents (2,645 women) in pregnancy in the USA, steroids and hydroxychloroquine were the most frequently used agents in pregnancy (48.4% and 27.1%, respectively). The rates for biologic agents showed an increase from 5% in 2001 to 16.6 % in 2012. Table 3 lists the common peri-pregnancy implications of drugs used in SLE[16].

Conclusion

One-third of SLE women develop complications. In more severe SLE, there is a higher chance of fetal complications. Over the recent decades, the proportion of pregnancies resulting in live birth has increased ($p = 0.024$)[17].

Educating patients and their families about appropriate contraception until the disease is stable to permit a planned pregnancy is essential, as they have the same fertility rates as their healthy counterparts. The disease is not in itself a contraindication to pregnancy unless associated with pulmonary hypertension and renal failure.

To achieve a good outcome, women should be in stable health and have a multidisciplinary team input from the Rheumatologist, Obstetrician and other specialists in the peri-pregnancy period. SLE must be monitored as a high-risk pregnancy all throughout the antenatal, intrapartum and postpartum period with regular assessment of SLE disease severity. Improved pregnancy outcomes have been noted with the use of low dose aspirin, heparin and HCQ and suitable disease modifying medications.

Appendix: Table 1: Fetal outcome in SLE

	Relative risk	95% CI
Miscarriage	1.51	1.26-1.82
Congenital anomalies	2.63	1.93-3.58
Live birth rate	1.38 in controls without SLE	
Preterm	3.05	2.56-3.63
Preeclampsia	1.91	1.44-2.53
Hypertension complicating pregnancy	1.99	1.54-2.56
Fetal growth restriction	1.69	1.53-1.88
Caesarean section	1.85	1.63-2.10
Neonatal intensive care	2.76	2.27-3.35
VTE	11.3	6.05-21
Post-partum infection	4.35	2.69-7.03

Table 2: Investigations for SLE severity & other autoimmune associations

Autoantibody panel	Haematological SLE	Renal SLE	SLE flare	Co-morbid conditions
Antinuclear antibody	Complete blood count	24-hour urine protein	ESR	Comprehensive metabolic panel
Anti-ds DNA	Coombs' test	Urinalysis	C-reactive protein	Lipid profile
Anti-Sm	Prothrombin time/INR	Serum creatinine	C3	Homocysteine
Lupus anticoagulant	Fibrinogen	(Cr)	C4	Thyroid profile
Anti-SSA/Ro	Partial thromboplastin time mixing studies	Spot urine Protein/Cr ratio	CH50	

Anti-SSB/La				
Anti-cardiolipin antibodies (IgG, IgM, IgA)				
Anti-beta 2 glycoprotein 1 antibodies				
Anti-RNP				
Anti PRL antibody				

Table 3: Common peri-pregnancy implications of drugs used in SLE

	Peri Conception	First Trimester	Second / Third Trimester	Breastfeeding
Prednisolone Methylprednisolone	YES	YES	YES	YES
Hydroxychloroquin	YES	YES	YES	YES
Methotrexate <20mg/week	Stop 3 months in advance	No	No	No
Sulphasalizine(SSZ)with 5mg folic acid	YES	YES	YES	YES
Azathioprine AZA <2mg/kg/day	YES	YES	YES	YES
Cyclosporin	YES	YES	YES	YES
Tacrolimus	YES	YES	YES	YES
Cyclophosphamide,	No	No	No	No
Mycophenolate mofetil	Stop 6 weeks in advance	No	No	No
IVIG	YES	YES	YES	YES
Infliximab	YES	YES	Stop at 16 weeks	YES
Etanercept	YES	YES	Second but not third	YES
Adalimumab Certolizumab	YES	YES	Second but not third	YES
Rituximab/ Tocilizumab	Stop 6 months in advance	No	No	No Data
Golimumab /Other Biologics	No	No	No	No Data

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NEWSLETTER Obstetric Medicine

Immunomodulators in Pregnancy and Lactation

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Introduction

Autoimmune diseases like Rheumatoid arthritis (RA), Systemic lupus erythematosis (SLE) and Inflammatory bowel disease (IBD) often occur in women of child bearing age. With the availability of a range of immunomodulators for treatment of these disorders, more women are achieving remission and are in a position to plan for pregnancy. In pregnancy and lactation, we should be guided by the relative benefits and risks to the mother and the fetus while we prescribe these medications. As the disease activity per se may have adverse maternal and fetal outcome, as much as the drugs, it is important for us to optimise the therapy to minimise disease activity and maximise pregnancy outcome.

Most of the data available about these drugs is based on animal studies, individual case reports and observational cohorts, as randomized controlled trials of medication safety in pregnancy and lactation are sparse because of ethical issues. No drug is completely safe in pregnancy but some medications may elicit fewer safety concern. Being well informed about the commonly used drugs from this class, helps in preconceptional counseling, management of patients who inadvertently become pregnant while undergoing therapy and wish to continue the pregnancy, and to manage those who have disease flares in pregnancy while on treatment.

The USFDA classification system for drugs in pregnancy which is in vogue, where letters are assigned to each drug depending on the safety profile (A-D & X) has some caveats such as it is not descriptive and the letters which are assigned at the time of approval is not subsequently modified with emerging data after clinical use. Hence this is being replaced by the Pregnancy & Lactation labeling rule (PLLR) 2015 in which the system of assigning a letter will be replaced by narrative sections on the drugs used in pregnancy, lactation and infertility. But because of our familiarity as of now with the earlier system we would continue to use it in this article.

Women who are attending the antenatal clinic may be on one or a combination of these drugs for indications such as connective tissue diseases, IBD, transplant recipients, multiple sclerosis, dermatological disorders and newly diagnosed breast cancer during pregnancy.

Some of these drugs now have been proven to be very safe or have minimal side effects in pregnancy, with our clinical experience. Some are absolutely contraindicated and between these two groups we have some drugs which can be used if the benefit overweighs the risk. There are some drugs with safety profile we are not sure of. This article is a brief review of the commonly used immuno modulators.

Hydroxychloroquine (HCQ): (CatC)

It is an antimalarial agent, which is commonly used in many autoimmune disease. HCQ can cross the placenta and the concentration in cord blood is approximately equal to maternal concentration, but excretion into breast milk is very low. It is not known to cause fetal toxicity in therapeutic doses. In women who are on the drug discontinuing it has been known to be associated with flares, so the drug should be continued during the pregnancy.

Sulfa Salazine(SSZ): (CatB)

There is sufficient data in favour of safe use of SSZ in pregnancy because of its many decades of use in IBD. Sufasalazine may cause folate deficiency because it inhibits dihydrofolate reductase and the cellular uptake of folate, and can cause an increase in the risk of neural tube defects, oral clefts and cardiovascular defects. This can be overcome by use of concomitant folate (5mg/ day) supplementation and an optimum dose of SSZ less than 2gm/day. Sulfapyridine, a metabolite of sulfasalazine can cross the placenta, displace bilirubin from albumin and possibly lead to neonatal jaundice. This may be a concern in preterm babies, hence it would be better to discontinue the drug during lactation, if the baby is preterm and babies with history of jaundice, for one or two months. Sulfapyridine levels in breast milk were found to be approximately 30 to 60% of those in the mother's serum, but it does not cause risk to healthy fullterm infants. Except in the setting of prematurity, hyperbilirubinemia or other acute stresses, sulfasalazine is considered safe during lactation.

Low Dose Aspirin

It is an analgesic and an anti-inflammatory agent. Low dose aspirin (81mg/day) is used as a part of management of APLA and prevention of hypertension and preeclampsia It does not have significant risk of bleeding either in the mother or in their babies. It can be continued throughout pregnancy.

NEWSLETTER Obstetric Medicine

Immunomodulators in Pregnancy and Lactation

NSAIDS (CatB/D)

NSAIDS may cause infertility through "luteinized unruptured follicle syndrome" or blastocyst implantation impairment. NSAIDS use during the 3rd trimester may cause greater risk. NSAIDS may cause olighydromnios due to its effect on the fetal kidney and may cause premature closure of the ductus arteriosus because they are prostaglandin synthetase inhibitors. These two effects are reversible after discontinuation of NSAIDS. High dose aspirin usage during 3rd trimester may increase the risk of fetal or neonatal bleeding or bruising via inhibition of platelet function.

Glucocorticoids: (CatB)

Corticosteroids because of its structural variability affect the mother and fetus differently. Beta-methasone and dexamethasone cross the placenta and have direct effect on the fetus because they are not well metabolized in the placenta.

Most other corticosteroids are metabolized in the placenta and only <10% of the active drug reaches the fetus.

Prednisolone is one of the important drugs used in the treatment of rheumatological disorders and can be used safely when indicated.

Glucocorticoid therapy during pregnancy may increase the risk of premature rupture of the membranes (PROM).

Steroid usage may increase the risk of cleft palate from 1 in 1000 in general population to 3 in 1000. This small increase in risk should be weighed against the need to treat active disease in the mother.

In the mother, steroids may increase the risk of pregnancy induced hypertension, gestational diabetes, osteoporosis and infections.

Supplementary calcium and vitamin-D are important in women with connective tissue disease, particularly those receiving steroids.

If a woman is on more than 7.5 mg of prednisone per day for more than 2 weeks parenteral steroids should be administered to cover the stress of labour & delivery, regardless of the route of delivery.

Azathioprine: AZA (CatD)

It is a commonly used immunosuppressive drug for the treatment of RA, SLE, organ transplantation and inflammatory bowel diseases.

It can be safely used in pregnancy because the fetal liver lacks the enzyme that converts azathioprine to its active metabolite. Some studies shows that azathioprine may cause preterm delivery and intra uterine growth restriction.

Azathioprine excretion is very low in breast milk and it is not contraindicated in lactating mothers.

Tumor Necrosis Factor Inhibitors:(CatB)

These biological agents (eg: etanercept, infliximab, adalimumab, certolizumab) are used in the management of RA, ankylosing spondylitis, inflammatory bowel disease and some skin disease. They are not teratogenic in animal studies. They do not cross into breast milk. It is better to discontinue infliximab by 21 weeks, adalimumab by 28 weeks and etanercept by 30-32 weeks to avoid significant drug levels in neonates. Certolizumab can be safely continued throughout pregnancy, because this drug level in neonatal cord blood is low to undetectable. In infants exposed to TNF inhibitors in utero, live vaccines should be avoided for the first six months of life. They can follow a standard vaccination schedule for inactive vaccines.

Intravenous Immunoglobulins

Use of immunoglobulins is safe in pregnancy. IVIG crosses the placenta after 30-32 weeks of gestation. There are occasional reports of hemolytic disease of the newborn and transmission of hepatitis C. It may be beneficial in patients with primary or secondary antibody immunodeficiencies, autoimmune diseases and for gestational therapy of neonatal hemochromatosis.

Ciclosporin and Tacrolimus: (Cat C)

These drugs are commonly used in post organ transplant patients.

These are calcineurine inhibitors and are safe in pregnancy. There are some reports of preterm births and FGR. The drug levels should be regularly monitored and the dose needs to be increased if required. The risk of hypertension is increased with Ciclosporine and diabetes with Tacrolimus, hence mothers should be monitored for this. The renal functions should be monitored as well. The other drug in this class, Sirolimus should be avoided. Both drugs are safe in lactation.

Cyclophosphamide: (Cat X)

It is an alkylating agent, commonly used for the treatment of malignancies, lupus nephritis and various

forms of vasculitis. It is contraindicated in pregnancy, as it can produce congenital anomalies, the risk of which is as high as 15-20%. It must be discontinued at least 3 months prior to conception. It may be used in 2nd and 3rd trimester pregnancy for life-threatening maternal disease and in chemotherapy for breast carcinoma and other malignanciies. It should be avoided during lactation.

Methotrexate: (CatX)

This folic acid antagonist with 15% risk of congenital malformations and risk of miscarriage should be discontinued at least three months prior to conception. Even after discontinuation, folic acid supplementation should be continued until conception and through out pregnancy. In those women who have unplanned pregnancy while on the drug and want to continue the pregnancy, counselling should be done and 5 mg folic acid supplementation should be continued.

Mycophenolate Mofetil (MMF): (CatX)

It is a commonly used drug in organ transplantation and in patients with SLE. MMF is teratogenic. It can cause spontaneous miscarriages and specific malformations like cleft lip and palate, microtia with atresia of external auditory canal, micrognathia and hypertelorism. Women of childbearing age should be counselled to have planned pregnancy while on this drug. Azathioprine is a safer alternative. Women should be switched from MMF to Azathioprine at least 3 months prior to conception. It is contraindicated in lactating women.

Leflunomide: (CatX)

It is contraindicated in pregnancy and lactation because of its marked teratogenecity. Effective contraception should be adviced for women of childbearing age for whom Leflunomide is prescribed. Conception should be delayed for 2 years after stoppage of Leflunomide. If the woman wishes to conceive while on the drug earlier, she should be advised to discontinue it and cholestyramine should be administered to reduce the serum level to safe range. (8 gms orally 3 times daily for 11 days). The elimination of Leflunomide can be confirmed by estimating drug levels 2 weeks apart. If plasma levels are >0.02mg/L, additional cholestyramine treatment is indicated.

Drugs of unknown risk

Some biologic agents have insufficient evidence related to the risks associated with their use in pregnancy . Occasionally it is necessary to continue those medications during pregnancy,from the point of mother's health. In these situations the mother should be counselled regarding the potential risks for decision making. These agents include;

- Anakinra
- Rituximab
- Abatacept
- Tocilizumab
- Tofacitinib

These agents are to be avoided during both pregnancy and lactation unless the mother's health is critically dependent upon these medications.

Conclusion

Though all immunosuppressants and modulators have safety concerns in pregnancy, the extent of it is different with each drug. If the disease is mild it can be managed without medications or when required, with low dose steroids alone. NSAIDS can be used safely, except late in last trimester. In moderate to severe disease, HCQS, steroids, AZA, CSA and tacrolimus may be used. In severe disease, high dose steroids, AZA are the drugs of choice. TNF alpha inhibitors can be used if indicated though the data is limited. Cyclophosphamide can be used in later months of pregnancy if it is an absolute necessity. MTX, LEF and MMF is absolutely contraindicated and when the women is on these drugs appropriate counseling should be done prior to conception or when there is an unplanned pregnancy.

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NEWSLETTER

Obstetric Medicine

SOCIETY OF
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Aims and Objectives

- To establish a forum for exchange and interchange of views and for enhancing fellowship among its members and to come out with evidence-based guidelines for management of medical disorders complicating pregnancy.
- To assist in the establishment of Obstetric Medicine as an important sub-specialty to advance clinical and scientific knowledge of medical illness complicating pregnancy.
- To promote research and training in Obstetric Medicine.
- To foster collaboration with other regional and international societies interested in Obstetric Medicine.
- To carry out all such activities as would contribute to the promotion of Obstetric Medicine.
- To promote formation of patient forums.

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