

ABSTRACT

Pregnancy in patients with connective tissue diseases specially SLE and RA is a challenge to the physician. RA usually improves during pregnancy, to flare up immediate post partum where as SLE usually flares up during pregnancy. The general principles to be followed are: pregnancy to be planned when the disease is quiescent for six to twelve months; minimum amount of medication should be applied to balance the risk and benefit ratio; potentially teratogenic drugs like methotrexate and leflunomide to be stopped three to six months prior to conception. Leflunomide if taken within two years is to be washed by cholestyramine. Sulfasalazine, hydroxychloroquine and azathioprine are safe during pregnancy. Corticosteroid can be used in low doses ~ 10 mg /day. NSAIDs to be avoided in third trimester. Biologics have no proven teratogenic potentials but there is paucity of safety data. As such it is recommended that Abatacept, Rituximab and Tocilizumab to be withheld prior to pregnancy; however TNF inhibitors may be continued until conception. During lactation NSAIDs if required should be short acting Ibuprofen just after feeding. Low dose corticosteroids, sulfasalazine, hydroxychloroquine, and azathioprine are safe in lactation. Anti TNF agents can also be given during lactation.

KEY WORDS

Biologics, DMARDs, lactation, pregnancy, rheumatoid arthritis, SLE

INTRODUCTION

Majority of women with autoimmune diseases desiring pregnancy usually have safe and relatively uncomplicated pregnancy. Major complications of DMARDs therapy during pregnancy are pregnancy loss, congenital anomalies and intra uterine growth restriction. Risk of preterm birth before 37 weeks is around 33% in case of systemic lupus erythematosus (SLE) compared to 5 to 10 % in the general population. Regarding RA, about 75 % of patients experience reduction of disease activity by the end of first trimester and about 20 – 30 % of pregnant rheumatoid arthritis (RA) patients will need medications to control disease activity.

There are major modulation of the innate and humoral immune system of the mother during pregnancy possibly induced by increasing level of progesterone.¹

In pregnancy, there is a shift of helper T cells towards Th₂ dominant state possibly by increasing levels of progesterone. SLE being a Th₂ predominant state, usually

exacerbate during pregnancy. Whereas, Th₁ mediated autoimmune diseases like RA, psoriasis, and multiple sclerosis improve during pregnancy.^{2,3}

Most studies suggest that, chance of SLE flare during pregnancy and post partum is minimal if the patient has controlled or inactive disease at the time of conception. Women with SLE in remission have approximately 80% chance of having a live birth. However, patients should be counselled about the adverse fetal outcome; like preterm birth and pregnancy loss. As such, women with SLE and RA, do not have decreased fertility. In the meta-analysis of SLE Pregnancies, there is a higher rate of miscarriage, stillbirth (pregnancy loss before 20 weeks) and neonatal death.⁴ Main causes of these are increased SLE activity at the time of conception, hypertension, prior or ongoing lupus nephritis and anti-phospholipid syndrome. All these increase the risk of pregnancy loss by 2 to 4 times than general population.⁵

Main issue is the continuation or discontinuation of DMARDs. The principles should be,

1. Avoid potentially teratogenic drugs, like leflunomide, in women with child bearing age and to discontinue methotrexate, 3 months prior to planned pregnancy.
2. Plan the pregnancy when the disease is quiescent for 6-12 months.
3. Minimum amount of medication should be applied to balance harmful effects of the drug on pregnancy and risk of under treatment.
4. Co-morbid conditions like hypertension, hyperglycemia should be controlled before conception.

CHOICE OF THERAPY

Use of medications must always balance the risk and benefit to both mother and fetus. Serious systemic rheumatological diseases which needs to be considered in this chapter, consists of mainly those in the child bearing age, like SLE, RA, Psoriatic arthritis, Polymyositis /Dermatomyositis, and vasculitides. US Food and Drug Administration (US FDA) rates each medications on the basis of its potential risk to the fetus. (Table 1)⁶

NON STEROIDAL ANTI- INFLAMMATORY DRUGS (NSAIDS)

They are FDA category C drugs with possible risk in the first and second trimester, but 'D' in the third trimester. Taking these drugs in first trimester has 1.8 fold increased

Table 1: FDA drug classification with respect to teratogenicity

- Category A: Controlled studies in women fail to demonstrate a fetal risk in the first trimester (and there is no evidence of risk in later trimester), and the possibility of fatal harm appears remote.
- Category B: Either animal reproduction studies have not demonstrated a fetal risk and there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect (other than decreased fertility) that was not confirmed in controlled studies on women in the first trimester (and there is no evidence of a risk in later trimesters).
- Category C: Either studies in animals have revealed adverse fetal effect and there are no controlled studies in human being or studies in women and animals are not available. Drugs in this category should only be given if safer alternatives are not available and if the potential benefit justifies the known fetal risk or risks.
- Category D: Positive evidence of human fetal risk exists, but benefits for pregnant women may be acceptable despite the risks, as if life threatening or serious disease for which safer drugs cannot be used or are ineffective. An appropriate statement must appear in the “Warnings” section of the labelling of drug in this category.
- Category X: Either studies in animal and human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience (or both) and the risk of using the drug in pregnant woman clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant. An appropriate statement must appear in the “contraindications” section of the labelling of drugs in this category.

risk of miscarriage. This increases to 5.6 fold if taken in the first week of conception and to an 8.1 fold risk if taken daily.⁷ Suppression of prostaglandins by NSAIDs may lead to poor implantation or decreased placental perfusion, both of which may lead to miscarriage. Several studies have found a possible link between NSAIDs use and congenital heart defect.⁸ NSAIDs in second and third trimester may decrease fetal renal perfusion leading to oligohydramnios which is reversible on cessation of the drug.⁹ NSAIDs should not be used in the third trimester due to premature closure of the fetal ductus arteriosus, which has been reported mainly after 27 weeks of gestation.¹⁰ As around 80-90% patients of RA, may have flare in post partum period and may need NSAIDs due to restrictions in use of DMARDs. In that case Ibuprofen is the preferred NSAID due to its relatively short half life and low penetration in the breast milk. The ideal time of intake of ibuprofen should be just after breast feeding, so that the blood level falls in time of next feed.¹¹

GLUCOCORTICOIDS

It is FDA category C drug with possible increased risk of cleft palate with doses more than 20 mg per day. Non fluorinated corticosteroids (prednisolone) are metabolised in the placenta by 11 beta hydroxysteroid dehydrogenase

to inactive forms, leaving less than 10% of the active drug to reach the fetus.¹² Thus, it is the ideal glucocorticoid when treating the mother. On the contrary, fluorinated corticosteroids like betamethasone and dexamethasone will cross the placenta with direct effects on the fetus.¹³ This is the ideal drug to prevent congenital lupus when the mother is positive for anti Ro/ La antibodies. Recent reports suggest, betamethasone may be preferred over dexamethasone because it may offer better long term neuro-developmental outcomes for the fetus.¹⁴ Corticosteroids whenever required should be used in lowest possible dose, preferably less than 10mg per day, as they carry risk of steroid induced hyperglycemia and even frank gestational diabetes as well as osteopenia osteoporosis, and hypertension in the mother. In a meta-analysis looking at birth defects after maternal exposure to corticosteroids, incidence of cleft palate was found to be 3 fold higher than in normal population. There are also isolated reports of neonatal cataract and adrenal suppression which may be dose dependent.¹⁵

In lactating mothers taking corticosteroids, level in the milk is less than 0.1% of the total prednisolone dose ingested. So mothers taking low dose prednisolone (less than 10 mg per day), the blood level is less than 10% of infant's endogenous cortisol production, which is of little clinical significance. However exposure may be minimised if nursing is done 3-4 hours after a dose is taken, because the peak level in the breast milk occur about two hours after a dose is taken and declines rapidly.¹⁶

HYDROXYCHLOROQUINE (HCQ)

It is a FDA category C drug. This drug is relatively safe during pregnancy and need not be discontinued during pregnancy, particularly in patients with SLE and SLE with Anti Phospholipid Syndrome. There are some isolated reports of ocular toxicity in infants born to mothers receiving these group of drugs, particularly chloroquine.^{17,18} A study of cardiac conduction in exposed infants found no abnormalities.¹⁷ Several larger studies have found no increase in fetal abnormalities among infants exposed to daily HCQ.¹⁹ In SLE patients, discontinuation of HCQ early in pregnancy is associated with flare and decreased gestational age.

In nursing mothers, HCQ is quite safe as it is secreted in very low quantity in breast milk. With a maternal dosing of 6 mg/kg/day, a fully breast fed infant would ingest around 0.2 mg/kg/day of HCQ.¹⁸ The American academy of paediatrics has designated HCQ as compatible with breast feeding with only minimal risk to the infants.

SULFASALAZINE(SSZ)

It is a FDA category B drug and is among the most preferred drugs during pregnancy requiring ongoing disease modifying drugs. Though it can lead to reduced fertility in men due to oligospermia and reduced sperm motility, it has no effect on fertility in women.²⁰ Most of the data of safety of SSZ in pregnancy comes from studies in inflammatory bowel disease. It can cause folate deficiency as it inhibits the enzyme dehydro folate reductase. So the

520 usual folic acid requirement during pregnancy should be doubled from 800 micro gram daily to prevent neural tube defect in fetus. Another important issue is the toxicity of its active metabolite sulfapyridine, which can cross the placenta and can displace bilirubin from albumin and can cause neonatal jaundice.²¹

In nursing mothers, it is advisable to consider restriction in the use of SSZ in preterm or jaundiced baby for 1-2 months. In usual cases it can be used safely in pregnancy.

AZATHIOPRINE(AZA)

It is a FDA category D drug, but still considered one of the safest immunosuppressive drug during pregnancy. Several studies in patients of SLE, inflammatory bowel disease(IBD) or solid organ transplants have documented no risk of congenital anomalies; however there are reports of preterm birth and growth retardations. Though AZA crosses the placenta, drug levels are low in the infants and prospective studies have not reported increased neonatal infection. Benefits of disease suppression far outweigh the potential risk of hazard.

Regarding breast feeding while on AZA, WHO working group on drugs and human lactation discourages its use though the level in breast milk is insignificant.^{22,23}

METHOTREXATE(MTX)

It is a class 'X' FDA drug and a known teratogen leading to dysmorphic facial features, skull and limb abnormalities and growth retardation known as 'aminopterin syndrome'. Main toxicity is in the first 8 weeks of gestation. In women contemplating pregnancy MTX should be stopped at least 3 months before conception and folic acid supplementation throughout pregnancy is recommended.^{24,25} A study published in 2014 described an increased risk of major birth defects and spontaneous abortion in women exposed to MTX, at dosages typically used in rheumatic patients, only in the postconception period, while no abnormalities were noted in women exposed before conception.²² For its potential embryotoxicity and teratogenicity in animals and human pregnancy, methotrexate discontinuation is suggested 3-6 months before conception.

As regards breast feeding, there are no well documented reports and It is contraindicated in lactation.

LEFLUNOMIDE

It is also FDA category 'X' drug and is not recommended in pregnancy and lactation and should not be prescribed in women of child bearing age. It has been associated with fetal abnormalities in rats. In women treated with leflunomide wanting to conceive, medication should be stopped immediately and cholestyramine wash out to be given at doses of 8 gm thrice daily for 11 days. These should be followed by checking the blood level, which should be less than 0.02 mg/L, which is usually safe. Based on its long half-life, cholestyramine washout is needed in any women upto two years after stopping the medication, as recommended by a panel of experts.²⁶

As data regarding effects of leflunomide in infants is not

available, it is not recommended and is considered unsafe during lactation.

MYCOPHENOLATE MOFETIL (MMF)

It is FDA category C drug. MMF is reversible inhibitor of inosine monophosphate dehydrogenase. It is now being increasingly used for the treatment of autoimmune diseases, particularly lupus nephritis, vasculitis, scleroderma lung syndrome.

In addition to reports of teratogenicity in experimental animals, there are case reports and registry studies of teratogenicity in human.²⁷ MMF readily crosses the placenta and there are reports of increased rate of spontaneous abortion and around 25% rate of congenital malformation.²⁶ There is a classical syndrome of MMF embryopathy consisting of tetrad "EMFO"

E – ear – microtia and auditory canal arrest.

M – mouth – cleft lip and palate.

F – fingers – brachydactyly of 5th finger and hypoplastic toe nails.

O – organs – cardiac, renal, CNS, diaphragmatic, ocular

US FDA has recently issued a blackbox warning based on this data.²⁸ Use of reliable contraception is necessary in women of child bearing potential. This drug should be discontinued 6 weeks prior to conception. If immunosuppression is required during pregnancy, AZA is a safer alternative.

Regarding lactation this drug is contraindicated as data on excretion into breast milk and effect of ingestion in infants is lacking.

CYCLOPHOSPHAMIDE (CYC)

It is FDA category ' D' drug with known risk to fetus. First trimester exposure to CYC carries a high risk like congenital anomalies of palate, limbs, and eyes as well as miscarriage.²⁹ In second and third trimester risk of congenital abnormalities are far lower. In life threatening flare of rheumatological diseases in 2nd and 3rd trimester, it can be used with consent from the patient because of the significant risk of pregnancy loss with or without CYC therapy.

In lactating mothers, there are reports of cytopenias in the infants in mothers taking CYC.³⁰

BIOLOGIC DMARDS

TNF Inhibitors

They belong to FDA category B drug, meaning thereby, no adverse effects were observed during exposure in pregnancy and lactation. Limited data on women exposed to TNF inhibitors suggest that, there is not an increase in fetal anomalies, pregnancy loss, pre-term birth.³¹ However there is a remote chance of VACTERL associations as one report of FDA database hypothesised. These consists of Vertebral anomalies, Anal atresia, Cardiac abnormalities, Trachea-Oesophageal fistula and/or Esophageal atresia, Renal agenesis and dysplasia, and Limb abnormalities.³²

Table 2: Summary of drug compatibility in pregnancy and lactation (BSR & NICE guideline)

	Compatible peri-conception	Compatible with first trimester	Compatible with second/ third trimester	Compatible with breastfeeding	Compatible with paternal exposure
Corticosteroids					
Prednisolone	Yes	Yes	Yes	Yes	Yes
Methylprednisolone	Yes	Yes	Yes	Yes	Yes
Antimalarials					
HCQ	Yes	Yes	Yes	Yes	Yes ^a
DMARDs					
MTX <20 mg/week	Stop 3 months in advance	No	No	No	Yes ^a
SSZ (with 5 mg folic acid)	Yes	Yes	Yes	Yes ^b	Yes ^c
LEF	Cholestyramine washout, no	No	No	No data	Yes ^a
AZA <2 mg/kg/day	Yes	Yes	Yes	Yes	Yes
CSA	Yes	Yes ^d	Yes ^d	Yes ^a	Yes ^a
Tacrolimus	Yes	Yes ^d	Yes ^d	Yes ^a	Yes ^a
CYC	No	No ^e	No ^e	No	No
MMF	Stop 6 weeks in advance	No	No	NO	Yes ^a
IVIG	Yes	Yes	Yes	Yes	Yes ^a
Anti-TNF					
Infliximab	Yes	Yes	Stop at 16 weeks	Yes ^a	Yes ^a
Etanercept	Yes	Yes	Second but not third	Yes ^a	Yes ^a
Adalimumab	Yes	Yes	Second but not third	Yes ^a	Yes ^a
Certolizumab	Yes	Yes	Yes ^a	Yes ^a	No data
Golimumab	No data	No data	No data	No data	No data
Other biologics					
Rituximab	Stop 6 months in advance	No ^f	No	No data	Yes ^a
Tocilizumab	Stop 3 months in advance	No ^f	No	No data	No data ^g
Anakinra	No	No ^f	No	No data	No data ^g
Abatacept	No	No ^f	No	No data	No data ^g
Belimumab	No	No ^f	No	No data	No data ^g

There are fallacies in the relative risk of the drug as the cause of the anomalies because, the reported cardiac and urogenital anomalies are also the most common seen in general population.

TNF inhibitors do not cross the placenta before 16 weeks of gestation, but after that, there is linear level of progressive increase of placental transfer. The rate of transfer is more, in case of infliximab than etanercept, adalimumab and golimumab. At immediate and 6 weeks post partum, the level of maternal and fetal infliximab are equal compared to 4% of maternal serum level in fetus, in case of etanercept.³³ As per BSR and NICE recommendation,³⁴

infliximab may be continued until 16 weeks and etanercept and adalimumab may be continued until end of second trimester. Etanercept and adalimumab should be avoided in 3rd trimester and stopped at 26 weeks. Certolizumab is compatible in periconception, throughout pregnancy. Golimumab has no data in periconception and throughout pregnancy.

There is minimal or no transfer of anti TNFs in breast milk and they can be safely allowed in lactation.

Rituximab

It is a FDA category 'C' drug. This drug crosses the

522 placenta as the pregnancy advances beyond 12 weeks of gestation. Several case reports of rituximab use during 2nd and 3rd trimester of pregnancy for acute life threatening maternal disease have not found association between ante-natal and post conception exposure to rituximab and adverse pregnancy outcome or congenital malformations.^{33,35} Neonatal cytopenias only have been reported. BSR and NICE guidelines recommend stoppage of rituximab 6 months prior to conception.³⁴

As per safety during lactation, no data are available regarding concentration in breast milk.

Tocilizumab

This is also a category 'C' drug, but its teratogenic potential is not definitely known. In the trials for FDA approval, the drug was found to increase risk of miscarriage. As per BSR and NICE³⁴ recommendations, the drug should be stopped 3 months before conception. Unintentional exposure in the 1st trimester is unlikely to be harmful.³⁵

There is no data to recommend tocilizumab during breast feeding.

Abatacept

It is FDA category 'C' drug. It crosses placenta in animal studies but did not produce any congenital malformations. There is limited human pregnancy experience. The manufacturer advises against pregnancy during therapy and recommends contraception for at least 10 weeks after stopping the drug. The elimination half life of abatacept is 25 days. However Pham et al recommends 18 weeks taking into consideration 5 times the half life of abatacept.³⁶

Regarding lactation, no data are available for excretion of abatacept in human breast milk. So, breast feeding can not be advised during breastfeeding.

Cyclosporin, Tacrolimus

They are category 'C' drugs. Both cyclosporine and tacrolimus are compatible throughout pregnancy in lowest effective dose. However there are reports of increase in premature delivery and low birth weight.³⁷ Mothers on cyclosporine and tacrolimus should not be discouraged from breast feeding. It is suggested to monitor blood pressure, renal function strictly during treatment period.⁴⁰

I.V. Gammaglobulin

This is used as a life saving therapy in cases of SLE flare, catastrophic APS and life threatening Vasculitic syndrome during pregnancy.

IVIg is compatible with pregnancy and breastfeeding.³⁸

Belimumab

There is insufficient data to recommend belimumab during pregnancy. Accidental exposure in 1st trimester is unlikely to be harmful. There is no data on belimumab use in breastfeeding.

Tofacitinib

It is FDA category 'C' drug. Tofacitinib is a small molecule Janus kinase (JAK) inhibitor, introduced in Indian market

in August 2016 though approved by FDA in 2012 for RA. Tofacitinib is a category C drug, but data regarding safety in pregnancy and lactation is still inadequate. In a recent review with over 1800 patients, no increase in incidence of pregnancy loss or congenital malformation than in general population was found.³⁹ However, according to EULAR recommendation, Current evidence is insufficient and in a planned pregnancy, treatment with tofacitinib should be stopped 2 months before conception.

CONCLUSION

Motherhood is a sacred and divine fulfilment of womanhood and no woman can be denied this divine gift. As a physician our aim will be to help her achieve this by modifying immuno-modulatory therapy and timing of conception. Both the pregnant woman and her partner should be educated about appropriate contraception and avoiding unplanned pregnancy. Pregnancy should be planned when the disease is in remission.

In some cases like SLE, Vasculitis, and other connective tissue diseases in pregnancy it is absolutely necessary to continue medications for best pregnancy outcome with respect to both mother and infant. It is the responsibility of the physician, and maternal-fetal medicine expert (high risk obstetrician) to use the most suitable DMARDs in accordance with the patient's desire during pregnancy, and initiating appropriate therapy post-partum to prevent severe flares taking into account the desire for breast feeding. For a comprehensive information regarding safety of drugs used in pregnancy and lactation EULAR guideline⁴¹ and BSR/NICE guidelines³⁴ are given in Table 2.

The Organisation of Teratology Information Services (OTIS) is a useful resource to women (<http://www.otispregnancy.org>).

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