REVIEW

Journal of Clinical Rheumatology and Immunology

OPEN ACCESS

Outcome of Pregnancy in Less Common Rheumatic Diseases: Inflammatory Myositis, Systemic Sclerosis and Vasculitis

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ABSTRACT

Pregnancy and fetal outcomes in patients suffering from systemic lupus erythematosus or antiphospholipid syndrome have been well described, as these are more common diseases and associated with frequent maternal and fetal complications. The data is scant about pregnancy-related morbidity and its outcome among less common rheumatic diseases like inflammatory myositis, systemic sclerosis (SSc), and vasculitis. Inflammatory myositis, vasculitis, and SSc are associated with higher risk of spontaneous abortions, preterm delivery, and intrauterine growth restriction (IUGR). Conception during active disease is associated with poor pregnancy outcomes, hence good control of disease is important. These diseases also increase risk of maternal complications like hypertension, preeclampsia, and antepartum hemorrhage. Due to rarity of these diseases, the individual experience of a physician is limited, thus it requires a collaborative team approach to have best outcome.

***Keywords*:** Pregnancy Outcomes; Myositis; Scleroderma; Vasculitis; Disease Activity; Rheumatic Diseases.

ABBREVIATIONS

AAV: Antineutrophilic cytoplasmic antibody associated vasculitis
ACE: Angiotensinogen converting enzyme
APS: Antiphospholipid antibody syndrome
GPA: Granulomatosis with polyangiitis
EGPA: Eosinophilic granulomatosis with polyangiitis
IIM: Idiopathic inflammatory myositis
ILD: Interstitial lung disease
IUGR: Intrauterine growth restriction
LBW: Low birth weight
MPA: Microscopic polyangiitis
PAH: Pulmonary arterial hypertension
RR: Relative risk
RDs: Rheumatic Diseases
SLE: Systemic lupus erythematosus
SSc: Systemic sclerosis
SRC: Scleroderma renal crisis
TAK: Takayasu arteritis
VLBW: Very low birth weight

KEY POINTS:

- Inflammatory myositis, vasculitis, and SSc are associated with higher risk of spontaneous abortions, preterm delivery, and IUGR.
- Conception during active disease is associated with poor pregnancy outcomes, hence good control of disease is important.
- These diseases also increase risk of maternal complications like hypertension, preeclampsia, and antepartum hemorrhage.
- Pregnancy is contraindicated in patients with significant pulmonary artery hypertension, cardiac dysfunction, and interstitial lung disease.

Received 16 January 2021; Accepted 10 March 2021; Published 4 May 2021

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DOI: 10.1142/S2661341721300019

INTRODUCTION

Rheumatic diseases (RDs) are much more common among women in childbearing age group [1]. Pregnancy tends to have a major effect on physiological and immunological parameters, which affects the disease course and activity. Changes in disease course as well as drugs have impact on pregnancy and its outcome. Pregnancy has varied impact on RDs, some of the diseases like rheumatoid arthritis improve, while others like systemic lupus erythematosus (SLE) worsen as pregnancy progresses. Most of the data available on fertility and pregnancy outcome is in SLE and antiphospholipid antibody syndrome (APS) as these are more common RDs and have frequent maternal and fetal complications [2].

Pregnant women with RDs comprise a high-risk population. Presence of RDs is associated with decreased fertility due to various factors like disease-related factors (impaired gonadal functioning, drugs avoidance of pregnancy) or due to psychosocial issues (personal choice, depression, loss of interest in sexual activity, anxiety, low self-esteem) [3]. Adverse outcomes are much more common, if conception occurs at the time of high disease activity. Complications include prematurity, intrauterine growth restriction (IUGR), low birth weight (LBW), neonatal deaths along with maternal morbidity including disease flares and mortality [2]. With recent advances in the management of RDs, the outcome of pregnancy has improved significantly over the years.

There is limited data regarding fertility and pregnancy outcomes in less common RDs, particularly inflammatory myositis, scleroderma, and vasculitis. This review will discuss pregnancy outcomes in these three rare diseases along with the effect of pregnancy on the disease.

MYOSITIS

Idiopathic inflammatory myositis (IIM) is a heterogenous group of disorder, which affects females more than males. It has a bimodal age of onset, with one peak in childhood, while other is in older adulthood. It also affects women of childbearing age group, although less commonly than SLE. In one case series, 14% of females affected with IIM were before or during reproductive age group [4]. The disease may start or have a flare in pregnancy or in the postpartum period [5,6]. Inflammation in myositis as well as use of drugs like corticosteroids and tacrolimus can increase risk of hypertension and diabetes, which can have a negative impact on pregnancy [7].

Effect of myositis on pregnancy

Pregnancy has been rarely reported in patients after the onset of disease. Published case series are of 2–26 pregnancies [7,8]. Nagy-Vincze M et al. in a multicentric study from China reported 26 pregnancies after disease onset [9]. Similarly, Gupta et al. in a single center study from India evaluated 81 IIM patients with median disease duration of 4 years (interquartile range 2–9 years), 63 patients had conception before disease onset, resulting in 205 pregnancies and 155 live births over 315.2 patient-years of follow-up. In contrast, after disease onset, only 24 pregnancies occurred in 7 women over 77.5 patient-years and of these 6 resulted in live births, 16 into spontaneous abortions, and 2 were induced abortions. Obstetric complications (relative risk [RR] = 7.6; $p < 0.0001$) and fetal complications (RR = 2.7; $p = 0.002$) occurred more frequently in pregnancies after the onset of disease, although there was no difference in maternal complications. Conception after the onset of myositis had higher risk of abortion (RR = 3.6; $p < 0.0001$) [10]. The reason for low conception rate could be multiple: serious disease with physical handicap, so patients do not plan to have pregnancy, late age of onset so they may have already completed their family, presence of interstitial lung disease (ILD) may be a relative contraindication for pregnancy. No prospective data on fertility in patients with IIM is available.

High disease activity at conception, seems to be associated with higher complications as compared to the inactive disease [8]. However, serious maternal complications are rare in patients with myositis.

Zhiqian Zong et al. reported 144 pregnancies in 62 women with myositis and found that pregnancy after disease onset had significantly higher risk of either preterm delivery or spontaneous abortion as compared to those before disease onset (36.4% vs. 9.3%, $p = 0.0026$) [5]. Pinal-Fernandez et al. in a retrospective cohort of 51 patients with 102 pregnancies, found no difference in maternal or fetal complications in pregnancies before or after disease onset [11]. Chen et al. in a study with 17 pregnancies in patients with IIM found an increased prevalence of hypertensive disorders in pregnancy, antepartum hemorrhage, and cesarean deliveries [12]. Kolstad et al. in a nationwide dataset from the United States of 853 pregnancies in women with myositis over 15 years in comparison to controls found that pregnant

patients with IIM are at an increased risk of hypertensive disorders of pregnancy (20.9% vs. 7.4%; $p < 0.001$) and have higher length of stay in hospital (mean of 4.3 ± 0.07 days compared to 2.5 ± 0.01 days in controls; $p > 0.001$), but there was no difference in prelabor rupture of membrane (PROM), IUGR, or rate of cesarean section [13].

Effect of pregnancy on myositis

A few case reports suggest pregnancy to be a triggering factor for IIM [6]. However, another study has shown improvement in disease activity during period of gestation [11]. Thus, the data is limited and prospective studies are required to know the effect of pregnancy on IIM.

VASCULITIS

Vasculitis is a disease characterized by inflammation of blood vessels and the clinical picture depends on size of vessel involved. Vasculitis predominantly affects adults of older age group. It is also more common in men as compared to women except for Takayasu arteritis (TAK). Still all types of vasculitis can affect women of reproductive age group. Since TAK and Behcet's disease, occur more often in reproductive age group, more data on pregnancy outcomes is available in these two diseases.

As is true for other RDs, pregnancy outcome seems to be better, if conception occurs at the time of inactive disease. Presence of end organ damage and high vascular disease activity are associated with poor maternal and fetal outcomes [14]. Although there are no studies that have directly looked at fertility in these patients, but in general, women who conceive after developing the disease, have a higher rate of pregnancy morbidity. Pregnancy loss has been reported in about 10% of cases in granulomatosis with polyangiitis (GPA), up to 20% in eosinophilic granulomatosis with polyangiitis (EGPA), 20–30% in Behçet's disease, and up to 25–30% of TAK [14]. In addition, pregnancy is associated with high rate of disease flare to the tune of 50% in some studies [16]. The important subtypes that would be discussed here include TAK, and antineutrophilic cytoplasmic antibody-associated vasculitis (AAV).

Takayasu arteritis

TAK is a large vessel vasculitis affecting aorta and its major branches. It predominantly affects young women in the second or third decade of life. It's the most common vasculitis affecting women of childbearing age. The main pathology in TAK is adventitial fibrosis leading to compromise of blood flow to involved organ or area. In addition, complications like cardiomyopathy, renal failure, and aneurysms also impact pregnancy outcomes.

Effect of TAK on pregnancy

Pregnancy in TAK is usually associated with increased risk of maternal complications like preeclampsia and hypertension along with fetal complications like prematurity, IUGR, and LBW babies. The overall rate of these complications is 40% as compared to 8% in general population [17,18]. In a large systematic review of 214 pregnancies in TAK patients, preeclampsia occurred in 45%, while prematurity was seen in 16% of pregnancies. Advanced vessel abnormalities like preexisting aortic disease and aneurysm were associated with higher maternal mortality and morbidity [19]. Another study of 156 pregnancies in TAK patients showed 17.9% preterm delivery and 12.8% pregnancy loss. In this study, use of corticosteroids was not associated with better outcome [20]. In a study from India, hypertension was the most frequent maternal complication, while LBW was the most common fetal complication [21].

Effect of pregnancy on TAK

Apart from hypertension and preeclampsia, other maternal complications include cerebral hemorrhage, congestive heart failure, aortic aneurysm, myocardial infarction, stroke, and renal insufficiency. Risk of some of these complications is maximum during peripartum period as fluctuations in regional blood flow occur at this time. Therefore, monitoring of central aortic blood pressure is recommended in patients of TAK with multiple vessel involvement. Data suggests that pregnancy is not associated with increased disease flares [22].

ANTINEUTROPHILIC CYTOPLASMIC AAV

AAV is an autoantibody-mediated necrotising vasculitis affecting predominantly upper respiratory tract, lungs, and kidneys. It includes GPA, EGPA and microscopic polyangiitis (MPA). It occurs mostly in older adults but can affect females of reproductive age group as well. Pregnancy occurring during active phase of disease or associated with a relapse has an unfavorable maternal and fetal outcome [23]. Though at present data is limited, with early diagnosis, better therapies, patients are surviving longer, therefore, in the coming time more data would become available.

Effect of AAV on pregnancy

As for other RDs, pregnancy outcome seems to be better if conception occurs during inactive phase

of the disease. Maternal complications reported, include preeclampsia, PROMs, spontaneous abortion, antepartum hemorrhage, and retroplacental hematoma, while fetal complications include preterm delivery reported in 35% of pregnancies and IUGR in patients with GPA [24].

In EGPA also preterm delivery is the most common complication of pregnancy, however fetal loss, IUGR, and cesarean delivery have also been reported [25]. Zakowski et al. reported 40% incidence of preterm delivery, while pregnancy loss was seen in 20% of patients with EGPA [26].

The data on the effects of MPA on pregnancy and vice versa is limited to case reports. The reported complications are maternal deaths, LBW, prematurity, and the occurrence of an MPA-like syndrome in the newborn [27–29].

Effect of pregnancy on AAV

GPA is associated with about 25% relapse rate during pregnancy [30]. Flare features include diffuse alveolar hemorrhage, vasculitic skin rash, subglottic stenosis, and deterioration in renal function. It's difficult to differentiate between preeclampsia and renal relapse of GPA. Points that might favor disease relapse are extra renal disease in skin, joints, lungs, and rise in titres of autoantibodies [31]. In EGPA and MPA rarely, vasculitic complications have been reported during pregnancy [25].

Overall vasculitis is associated with increased pregnancy morbidity thus control of disease activity before conception and during pregnancy can improve the chances of successful outcome. Therapy with low-risk immunosuppressive agents like azathioprine, intravenous immunoglobulin, and prednisone should be used during pregnancy. As a rule, active disease is associated with an adverse pregnancy outcomes, so it is important to control underlying inflammation before pregnancy. Steroids are safe but have slightly increased risk of preterm delivery and IUGR. Azathioprine has been used most often due to years of experience without any significant maternal and fetal complication [32]. Intravenous immunoglobulin too is safe in pregnancy, however, due to high cost it is used rarely.

SYSTEMIC SCLEROSIS

SSc or scleroderma is an autoimmune disease characterized by inflammation, fibrosis, and vasculopathy. The factors involved in the development of SSc include immune activation, vascular damage, and excessive synthesis of extracellular matrix, and collagen leading to fibrosis. It mainly occurs in fifth or sixth decade of life, although it can affect women in childbearing age group also. The clinical manifestations include Raynaud's phenomenon, skin thickening, pulmonary (pulmonary arterial hypertension [PAH], ILD), gastric (gastroesophageal reflux disease), renal (scleroderma renal crisis [SRC]), musculoskeletal, and cardiac disease. In addition to maternal and fetal complications, fertility too is decreased in scleroderma [33].

Effect of SSc on pregnancy

Pregnancy in SSc is a high-risk situation because of multisystem involvement. Different variants of the disease (diffuse SSc vs. limited SSc) have different impact on pregnancy. Among 91 pregnancies among 59 women with SSc, the rate of miscarriage was twice (24% vs. 12%) in diffuse SSc as compared to limited SSc [34].

The International Multicentric prospective study on PREgnancy in Systemic Sclerosis (IMPRESS) group of investigators studied 99 Italian patients with SSc over a decade and compared pregnancy outcomes with general population. Patients with SSc were more likely to have preterm deliveries (25%), IUGR (6%), and very low birth weight (VLBW) babies (5%). Among these 99 women, 18 had coexisting antiphospholipid antibodies, which might be a confounder suggesting that it may not be the disease itself that leads to poor outcome. Use of corticosteroids (odds ratio [OR] 3.63[1.12–11.78]) was associated with preterm deliveries, whereas folic acid supplementation (OR 0.3[0.1–0.91]) and antiscl70 antibodies (OR 0.26 [0.08–0.85]) were protective [35]. The biological plausibility of antiscl70 antibody positive patients having lesser fetal complications is not clear and may be related to the relatively worse prognosis in patients with other autoantibodies like RNA-pol3, fibrillarin, and Th/T0.

Another case-control study of 155 patients with SSc, found that the rate of spontaneous abortion was double as compared to general population [36]. Chakravarty et al. studied 504 deliveries that occurred in women with SSc in the United States, and found an increased risk of hypertension (OR 3.71), IUGR (OR 3.74), and increased length of hospital stay [37].

Effect of pregnancy on SSc

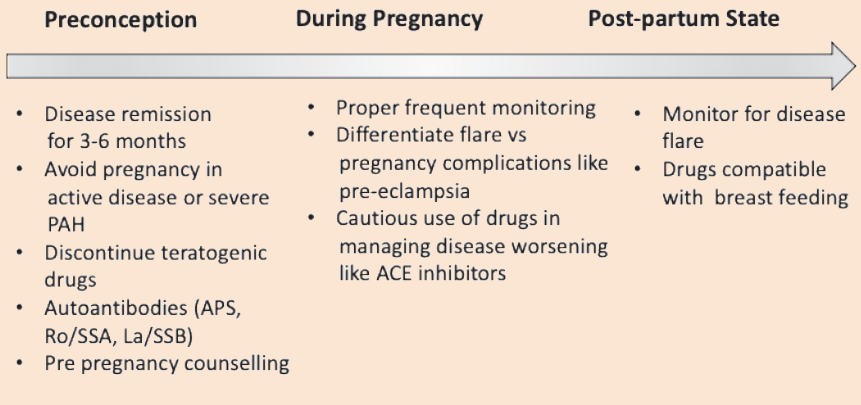
Though most of data shows hardly any impact of pregnancy on disease [37–39]. The IMPRESS study demonstrated that there was improvement in digital ulceration in 20% and Raynaud's phenomenon in 32%,

Table 1. Pregnancy outcomes in rheumatic diseases.

Disease	Maternal complication	Fetal complications
Myositis	Hypertensive disorders in pregnancy, antepartum hemorrhage, and cesarean deliveries, PROM [9,10]	Preterm delivery, spontaneous abortion, IUGR [9,10]
Vasculitis	Preeclampsia, hypertension, pregnancy loss, prepartum hemorrhage, retroplacental hematoma [24,25]	Prematurity, IUGR and low birth weight, spontaneous abortion, MPA-like syndrome [17,18,27–29]
Systemic sclerosis	Hypertension, increased hospital stay, pregnancy loss [37]	Preterm, IUGR and low birth weight, spontaneous abortion [37]

Note: IUGR: Intrauterine growth restriction; MPA: Microscopic polyangiitis; PROM: Prelabor rupture of membranes.

Figure 1. Considerations while planning pregnancy in rheumatic diseases.



while worsening was seen in as gastroesophageal reflux and dysphagia in 19% of patients. However, due to the small numbers involved, these findings need validation as in majority of the patients there was no change in disease activity during pregnancy [35].

Similarly, another study of 133 scleroderma pregnancies, found that 88% had stable disease, while 7% had improvement and 5% had worsening. One pregnancy-related maternal death was reported [40]. In a prospective study again stable disease was seen in 63%, improvement in 20%, and worsening in 18% [36].

SRC is the most severe renal manifestation occurring in about 5%–20% of cases with SSc [41]. Risk factors for developing SRC include diffuse skin disease, presence of anti-RNA polymerase III antibodies, absence of anticentromere antibodies, and use of high doses corticosteroids. It is indeed very difficult to distinguish SRC from eclampsia as cause of renal dysfunction in SSc during pregnancy. Indeed 7 of 9 patients initially thought to have preeclampsia actually had renal biopsy findings, which were more consistent with SRC. Steen et al. found SRC during pregnancy in 2% cases and all of them had early diffuse SSc [40]. Angiotensinogen converting enzyme (ACE) inhibitors are the drug of choice for SRC, however, they are contraindicated in pregnancy due to teratogenicity. Its use becomes mandatary when maternal risk exceeds fetal risk. Patients with SSc and active renal disease should be counselled regarding the high morbidity and mortality associated with pregnancy, especially when they have glomerular filtration rate <30 mL/min/1.73 m^2, proteinuria or uncontrolled hypertension [42].

PAH and ILD too have been associated with poor maternal and fetal outcomes. Moderate to severe PAH is an absolute contraindication for pregnancy and patients must be counselled regarding the same. Most of the studies do not show any progression in ILD during pregnancy, while some have shown increased incidence of preterm deliveries in patients with ILD [37–40].

CONCLUSION

RDs and pregnancy can affect each other thus it poses a challenge both for patient and the physician. Patients with

IIM, vasculitis, and SSc have increased risk of maternal and fetal complications. Preconception counselling is important to allay fear, modify drugs to drugs that are safe in pregnancy and to assess disease activity. Conception during stable or inactive disease has better outcome. With careful planning and a multidisciplinary team approach involving rheumatologist, obstetricians, and neonatologist, most women with RDs can have successful pregnancy.

CONFLICT OF INTEREST

All authors were involved in manuscript ideation and preparation. The authors declare that they have no competing interests. No funding was received.

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