

The Course of Rheumatic Diseases During Pregnancy

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ABSTRACT: Rheumatic diseases commonly affect women of childbearing age, when women may be contemplating pregnancy or they discover an unplanned pregnancy. Therefore, specific issues about pregnancy planning and management are commonly encountered in patients during these times. Knowledge of the effect of pregnancy on disease activity is important for counseling. This review summarizes recent data on the course of different rheumatic diseases during pregnancy and the postpartum period. Rheumatoid arthritis and systemic lupus erythematosus are the most commonly investigated diseases. Data are increasing about spondyloarthritis. Sparse data are available for other rheumatic diseases. Despite the differences in these diseases and the various courses these disease take during pregnancy, a common feature is that active maternal disease in the months prior to conception increases the risk of flares during pregnancy, which in turn can lead to adverse pregnancy outcomes. Therefore, maternal and fetal health can be optimized if conception is planned when disease is inactive so that a treatment regimen can be maintained throughout pregnancy.

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Rheumatic diseases tend to behave differently during pregnancy and the postpartum period; therefore, patients need to understand the specific risks related to the underlying disease itself. Nevertheless, most of the studies focused on the obstetric and fetal outcomes, while the disease course was considered as secondary outcome.

In this narrative review, we summarize the evidence about the course of different rheumatic diseases during pregnancy and the postpartum period.

INFLAMMATORY CHRONIC ARTHRITIS

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a systemic autoimmune disease that leads to chronic inflammation of the joints and other musculoskeletal structures. Without the use of disease-modifying agents, RA often leads to progressive deformities of the hands, feet, and larger joints. Over the past few decades, innovative treatments have led to better control of disease and significantly slower progression of joint damage.

Historically, pregnancy has been considered to have a beneficial effect on RA, with approximately 90% of women showing an improvement in symptoms [2]. These findings were shown mostly from retrospective studies, which lacked objective disease activity measures.

Modern prospective studies using validated measures of disease activity have revealed less impressive ameliorative effects of pregnancy on RA [2]. A recent systematic review of prospective studies using serial and objective evaluations of inflammatory disease reported that RA improved in 60% of patients through pregnancy and flared in 46.7% of cases after delivery [2]. As stated by the authors, the results of this meta-analysis are limited by different study design and patient population (disease duration, disease severity, demographic differences). Moreover, it should be considered that women with a more aggressive disease may be more inclined to consider pregnancy than in previous decades due to disease control achieved with innovative treatments.

The impact of antibody status on the risk of flare during pregnancy and the postpartum period has been less investigated. In the Dutch Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA) study, disease activity improvement during

Rheumatic diseases often affect women during their childbearing years, when women may be contemplating pregnancy or discover an unplanned pregnancy [1]. As such, specialized issues in pregnancy planning and management are commonly encountered in these patients.

For decades, women with rheumatic diseases had been advised against pregnancy, given the high rates of poor pregnancy outcomes, concern for disease flare, and lack of evidence for safe treatment options. With current advances in therapies, many patients can experience sustained periods of disease remission with less progressive disability and therefore may be more prone to consider pregnancy [1]. Accurate knowledge of the effect of pregnancy on the activity of rheumatic diseases is therefore important to enable a complete preconception counseling, particularly addressing the need for changes in therapy to avoid disease relapse and assure good maternal and fetal outcomes [1].

pregnancy was not associated with changes in levels of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA). However, patients who tested negative for RF and ACPA were less likely to experience a flare during pregnancy compared to autoantibodies-positive women [3]. In another prospective cohort, patients with active disease before and during pregnancy showed significantly higher levels of ACPA compared to patients with low disease activity during pregnancy [4]. Interestingly, among 75 prospectively followed RA pregnancies, in patients treated with tumor necrosis factors inhibitors (TNFi) before conception, the discontinuation of the TNFi early in pregnancy resulted in increased risk for disease flares during pregnancy [5].

JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of diseases characterized by arthritis emerging before the age of 16 years. Although the natural course of JIA is variable among the different subsets and may include sustained remission, more than one-third of all JIA is still active during adulthood, thus requiring treatment [6]. The dramatic changes in the prognosis resulting from the introduction of biologic agents have increased the number of JIA female patients planning to get pregnant [6].

Two retrospective studies, which were based on self-report questionnaires, revealed that JIA women in remission before conception remained in remission during pregnancy. Among women with active disease at baseline, 57–94% experienced amelioration and about 50% reported increased disease activity between 3 and 12 months postpartum [7,8].

Recently, prospective data from the Norwegian register (REvNatus), using validated disease activity measures, showed that almost 80% of the JIA women were in remission or had low disease activity during and after pregnancy. Disease activity, stable throughout the study period, increased 6 weeks postpartum compared to the first and third trimester but only 22% of women experienced a flare [6]. Of note, in this study the majority of patients had stable low disease activity, and many had planned pregnancies while effectively treated without discontinuation throughout and after pregnancy. This experience was different from the previous observations. Therefore, the ongoing treatment could have hidden the occurrence of postpartum flare.

It is worth noting that none of these studies analyzed the disease course according to different subsets.

Spondyloarthritis

Spondyloarthritis (SpA) is a heterogeneous group of chronic inflammatory arthritis affecting mainly the spine but also peripheral joints, entheses, and extraarticular sites (skin, uveitis, bowel). The SpA group includes axial SpA (axSpA; incor-

porating non-radiographic axSpA and ankylosing spondylitis), peripheral SpA, reactive arthritis, and psoriatic arthritis (PsA). Ankylosing spondylitis (AS) is termed the prototype of r-axSpA. The present review focuses mainly on AS (or r-axSpA) and PsA, the most frequent types of chronic SpA [9].

Women with SpA are often affected by the disease during their reproductive years, but robust, prospective data on disease activity during pregnancy are limited. Recently, prospective data from the RevNatus registry showed that the majority of women with r-axSpA had stable or low disease activity from preconception period to one year after delivery with a small increase in the second trimester [9]. Previous studies reported that axSpA tended to be stable or to get worse [10]. Only one small retrospective work showed that the majority of women with AS displayed a decrease in disease activity during pregnancy [11].

In a recent report of 61 pregnant women with axSpA, who were prospectively followed, the discontinuation of TNFi early in pregnancy was a risk factor for flare [5]. In non-radiographic axSpA patients, data on the disease course during pregnancy are not available. Regarding PsA, data are scarce. Two prospective

studies demonstrated improvement during pregnancy and deterioration in the postpartum period [7,12]. The first one was published in 1992, before the widespread use of biologic agents. That study included patients with relatively low disease activity and did not consider patients with polyarthritis or axial disease. Importantly, significant changes have taken place in the treatment strategies of PsA since then, and a substantial number of patients are now being treated with biologic therapies [7].

More recently, prospective data from the RevNatus registry showed that nearly 75% of 103 women with PsA were in remission or had low disease activity during and after pregnancy according to the Disease Activity Score 28-joint count C reactive protein (DAS28-CRP). Although somehow stable, disease activity tended to decrease during pregnancy and to increase within 6 months after delivery [12]. Small retrospective studies have later shown that PsA tended to be stable or improve during pregnancy [13,14]. Regarding psoriasis, the activity of skin involvement during pregnancy tended to improve or remain stable in most of the patients, while worsening in the postpartum period in less than 50% of cases [13]. Similar to axSpA, discontinuation of TNFi at conception is associated with an increased number of flares during pregnancy [14]. No data are available about the course of dactylitis, enthesitis, and axial involvement during PsA pregnancy.

CONNECTIVE TISSUE DISEASES

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that can affect almost any organ in the body with a strong female predominance and highest incidence during

childbearing age. Studies indicate that approximately 35–70% of women with SLE may experience a flare during pregnancy or after birth [15-19]. Most flares affect the mucocutaneous, musculoskeletal, and hematological (particularly thrombocytopenia) systems [15]. The nature of organ-specific lupus activity during the 6 months before conception seems to be predictive of the type of flare during pregnancy [16]. Some studies suggested an increased risk of flare during the third trimester or up to one year after delivery [17]. It is now well-known that high disease activity before conception increases the risk of flare during pregnancy. In a prospective observational study, a SLE Disease Activity Index (SLEDAI) score of 4 or more at 6 months before conception predicted adverse maternal outcomes (flares and preeclampsia), while disease flare during pregnancy predicted adverse fetal outcomes [18]. Recently, the Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus (PROMISSE) study showed that in 318 patients with mild-moderate active disease in the first trimester, severe flares in the second and third trimesters occurred in 2.5% and 3.0%, respectively [19]. Other factors that increase the rate of flares are discontinuation of disease-modifying medications, especially hydroxychloroquine, and an active glomerulonephritis at the time of conception [15]. Within the PROMISSE study, patients with previous kidney disease more often experienced reactivation of nephritis (11%) than those without previous kidney disease (2%) [15]. Low C4 was associated with renal flares, but not low C3 or positive anti-dsDNA alone [15]. More recently, in a Norwegian longitudinal follow-up of pregnancies in women with SLE (RevNatus registry), the majority of women had no or low disease activity at conception and during pregnancy and experienced an increase in disease activity at 6 and 12 months after delivery [20]. These data highlight that pregnant women with SLE have a better controlled disease during pregnancy than previously reported. A tight-control management and the use of medications that are safe during pregnancy can explain the improvement in the outcome of SLE pregnancies.

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by venous or arterial thrombosis and/or adverse pregnancy outcomes mediated by antiphospholipid antibodies (aPL) [21].

Even though APS was described as a unique disease, the distinction between thrombotic APS (t-APS) and obstetric APS (ob-APS) has been proposed recently. In fact, it was observed that some patients mainly experience obstetric manifestations, some patients mainly experience thrombotic manifestations, and some patients both. Different biological and clinical features of the vascular involvement and obstetric complications

could be the reason of this heterogeneous clinical phenotype.

For this reason it is difficult to have large homogeneous cohorts reporting outcomes in the different subsets. Moreover, talking about APS and disease activity during pregnancy means discussing the disease itself, considering that pregnancy can also increase the risk of thrombotic features.

In aPL-positive women, nearly 80% of anamnestic pregnancies (without any treatment) were complicated by adverse pregnancy outcome (APO). The use of standard treatment based on heparin and low dose aspirin have led to a surprising increased of live birth rate (77–87%) [22,23].

In the recently published European ob-APS multicentric registry, including 1000 patients and 3553 pregnancies, recurrent early miscarriage (< 10) was the most frequent manifestation [22]. Among obstetric complications, 27% were recurrent early miscarriage, 17% fetal loss, 18.5% stillbirth, 4.9% early PE, and 5.4% early intrauterine growth restriction. Although pregnancy outcomes have dramatically improved in APS, nearly 20% of pregnancies are still unsuccessful [24]. In fact, in recently treated pregnancies, premature birth seems to be the most frequent APO [22].

Risk factors for APO include history of thrombosis, associated autoimmune disease, hypocomplementemia, triple and double aPL positivity, positive lupus anticoagulant, high anti-body titers, and IgG isotype [21,23]. Although high antibody titers are associated with APO, low titers are also noted.

There is a growing body of evidence that patients with low titers have similar rates of APO, but not increased thrombotic risk [21].

It is still not clear whether women with positive aPL without clinical manifestations, the so called aPL carriers, carry an increased risk of APO and thrombosis. A recent multicenter retrospective study found similar rates of APO among aPL carriers and patients with definitive t-APS and ob-APS despite standard treatment [23]. This finding could be explained by the limited use of heparin in aPL carriers, despite the presence of a high risk aPL profile. In a multi-center cohort of pregnant aPL carriers, triple aPL positivity was shown to be an independent risk factor for APO [25].

In the general population there is an increased risk of thrombotic events during pregnancy because an induced thrombophilic state with a prevalence of 0.1% [26]. Therefore during pregnancy APS patients have an additional increased risk factor for thrombotic events, which are reported as high as 2–3% [21,22]. Whenever they take place, clots are mainly venous during postpartum and in patients with previous thrombosis [21,23]. It must be considered that APS also increase the risk of arterial thrombosis. In a recent retrospective study the majority of the thrombotic events occurred during puerperium, despite the use of adequate antithrombotic treatments. [23].

It is important to remember that pregnancy can be a trigger for a rare life-threatening condition, the catastrophic antiphospholipid syndrome (CAPS). CAPS is characterized by rapid appearance of multiple thromboses (mainly small-vessel thromboses) that lead to multi-organ failure with a high maternal and fetal mortality rate [27].

SYSTEMIC SCLEROSIS

Systemic sclerosis (SSc) is a rare and heterogeneous connective tissue disease (CTD) characterized by skin fibrosis, vasculopathy/vascular damage, and potential visceral impairment. Studies assessing disease activity during pregnancy concluded that the disease seems to remain stable [28,29]. Almost 61% of patients remained stable, and about 20% improved or worsened during pregnancy [28]. Regarding specific SSc symptoms, an improvement of Raynaud's phenomenon (32%) and digital ulcers (20%) was found during the second trimester [29], but it was only temporary. Skin thickening worsened in a minority of women (11–15%) after pregnancy, mainly in diffuse cutaneous SSc (dcSSc). There is a trend for worsening of esophageal reflux during the second and third trimester in 10–20% of patients, which could be partially related to physiological pregnancy changes [29]. Progression of organ involvement was not frequently found. In recent studies, a prevalence of 0–3% of renal crisis during pregnancy has been found [28]. Even so, patients with anti-Scl-70 and a disease duration less than 3 years have a higher risk of progression of internal organ damage during pregnancy or postpartum period [29]. Patients with severe cardiopulmonary or renal disease should be discouraged from getting pregnant, similar to patients with cardiovascular disease not related to SSc, due to the high risk of poor maternal and fetal outcomes. Pulmonary arterial hypertension is associated with 17–50% of maternal death in relation to severe hemodynamic complications in early postpartum [28].

OTHER CONNECTIVE TISSUE DISEASES

Other CTDs are less prevalent among the general population and even more during reproductive ages. This may explain why high quality and large cohort studies are lacking. However, due to the increasing delay of pregnancy in the general population, pregnancy is becoming an important issue for these women. Even though data are limited, it seems clear that the risk of flare and APO depends on disease activity before conception. Therefore, tight control, use of safe drugs during pregnancy, and a multidisciplinary team are necessary also in these CTD cases.

Undifferentiated connective tissue disease: Undifferentiated connective tissue disease (UCTD) is a term used in the presence of systemic autoimmune features not fulfilling criteria for any defined CTD. Two prospective studies comparing preg-

Table 1. Maternal disease activity in pregnancy in chronic inflammatory arthritis

Disease	Type of studies	Number of pregnancies (range)	Activity during pregnancy	Activity during postpartum	Predictors of disease activity
RA	Retrospective, prospective, metanalysis	237	40–90% improvement	46.7% increased disease activity	High disease activity (conception/1st trimester), ACPA and RF positivity, discontinuation of TNFi early in pregnancy; higher risk of active disease
axSpA	Retrospective, prospective	10–179	Stable disease activity, can get worse; higher disease activity II trimester	22–80% increased disease activity	Discontinuation of TNFi early in pregnancy; higher risk of active disease
PsA	Retrospective, prospective	20–108	75–80% remission/low disease activity	21–50% increased disease activity	Continuation of biologic agents: associated with a low level of disease activity and a low probability of flare during pregnancy
JIA	Retrospective, prospective	23–135	Stable or improved disease activity	Stable, even increased disease activity 6 weeks postpartum (22–50% flares)	–

ACPA = anti-citrullinated protein antibodies, axSpA = axial spondyloarthritis, JIA = juvenile idiopathic arthritis, PsA = psoriatic arthritis, RA = rheumatoid arthritis, RF = rheumatoid factor, TNFi = tumor necrosis factor inhibitors

Disease control should be achieved with treatment strategies that can be continued throughout pregnancy and lactation

nant and non-pregnant UCTD patients focused on disease activity subjects [30,31]. The first one showed a 24% flare rate

throughout the three trimesters and postpartum period [30]. The second study found a 32% rate of flare [31]. In both studies, the flares most frequently affected mucocutaneous

(malar rash) and musculoskeletal systems, but hematological (thrombocytopenia) and severe organ impairment (glomerulonephritis) have also been described. Castellino et al. [31] described an increased rate of evolution into a well-defined CTD from 12% in pregnant UCTD patients to 2% in non-pregnant UCTD patients.

Mixed connective tissue disease: Mixed connective tissue disease (MCTD) is a CTD with overlapping clinical features in the presence of a high titer anti-ribonucleoprotein (RNP) antibody [32]. Studies regarding disease activity in pregnant MCTD patients are limited due to the low prevalence of the disease and the fact that most patients evolve into a complete MCTD situation after childbearing age [32]. Since clinical evidence comes mostly from case reports, the magnitude of flares during pregnancy is not known. MCTD patients are said to have a modest risk of disease flare during pregnancy including severe internal organ impairment like renal crisis and pulmonary hypertension [32]. In a recent multicenter retrospective study among 203

Table 2. Maternal disease activity during pregnancy in connective tissue diseases and vasculitis

Disease	Type of studies	Number of pregnancies	Activity during pregnancy	Activity during postpartum	Risk factors for flares	Type of organ involvement
SLE	Retrospective, prospective	16–385	35–70% flares	Increase in disease activity at 6 and 12 months after delivery	Disease activity at conception discontinuation of HCQ; active nephritis	Mucocutaneous musculoskeletal hematological
APS	Retrospective, prospective	98–3553	Recurrent early miscarriage 27% Foetal loss 17% Stillbirth 18.5% Early PE 4.9% Early IUGR 5.4%	Thrombosis 2–3%	Thrombosis Autoimmune disease Triple aPL positivity High aPL titers, IgG aPL, LA Hypocomplementemia	
SSc	Retrospective, prospective	59–99	Stable; worsening reflux; improvement Raynaud's phenomenon	15% skin thickening Low risk of flare of major organ involvement	dcSSc; SCL-70+; disease duration < 3 years	Mucocutaneous gastrointestinal Less frequent: ILD, renal
UCTD	Retrospective, prospective	20–50	16%	12.7% 25% progression to a defined CTD		Mucocutaneous musculoskeletal hematological Less frequent: renal
MCTD	Retrospective case reports	7–9	11–50% onset during pregnancy; 25–33% flare			Hematological, musculoskeletal Less frequent: renal
SS	Retrospective	45	4.4%	10%		Mucocutaneous, hematological
IIM	Retrospective case reports	4–33	Flares related to active disease at conception 37% improvement 3.7–9% disease onset	0–12.5%	Active disease at conception	Musculoskeletal
Behçet	Retrospective	31–66	High variability 8.3–30% worsening, 60% improvement		Early onset disease	Mucocutaneous musculoskeletal thrombosis
Takayasu	Retrospective	8–214	3–5.8% Symptoms related to chronic damage and pregnancy changes in CV system	Symptoms related to chronic damage and pregnancy changes in CV system		Progression of renal disease, fever, elevated inflammatory markers, anemia Less frequent: aortic dissection, stroke
PAN	Retrospective case reports	2–8	Remission at conception, rare flare. Disease onset; 80–90% death rate		Active disease at conception	
SVV	Retrospective case reports	GPA: 8–48 EGPA: 6–26 MPA: 2–6	GPA: 40% 100% active disease at conception EGPA: 24% MPA: 67%		Active disease at conception	Internal organ involvement and life-threatening flare 20%

aPL = antiphospholipid antibodies, APS = antiphospholipid syndrome, CV = cardiovascular, EGPA = eosinophilic granulomatosis with polyangiitis, GPA = granulomatosis with polyangiitis, IIM = idiopathic inflammatory myopathies, IUGR = intrauterine growth restriction, LA = lupus anticoagulant, MCTD = mixed connective tissue disease, MPA = microscopic polyangiitis, PAN = panarteritis nodosa, PE = preeclampsia, SLE = systemic lupus erythematosus, SS = Sjögren's syndrome, SSc = systemic sclerosis, SVV = small vessel vasculitis, UCTD = undifferentiated connective tissue disease

pregnancies in MCTD, women with a concomitant diagnosis of obstetric APS, muscular and pulmonary involvement had worse fetal outcomes compared to those without [33].

Sjögren's syndrome: Sjögren's syndrome is an autoimmune disease characterized by lymphocytic infiltration of exocrine glands and possible multi-organ involvement that mostly affects women in their fourth and fifth decade of life. Various retrospective studies and case reports deal with pregnancy and Sjögren's syndrome but mostly focusing on obstetric outcomes [34]. A retrospective multi-centric case-control study reported two flare in 45 pregnancies: one thrombocytopenia and one cutaneous flare, leading to treatment change. A 10% of flares was found

one year after delivery, but not data about the characteristics of these flare were reported [34].

Idiopathic inflammatory myopathies: Idiopathic inflammatory myopathies (IIM) are a wide group of diseases characterized by proximal symmetric muscle weakness and, in some, cutaneous manifestations. Polymyositis and dermatomyositis are the most common forms of IIM with a disease onset from 25 to 34 years in 4–11% of patients [35]. Prospective studies are lacking. In a retrospective study with self-report questionnaires, disease activity did not seem to increase and a clinical improvement was found in 37% of patients during pregnancy [36].

Retrospective studies reported no flare during pregnancy, even when immunosuppressive treatment was withdrawn at the beginning of pregnancy [35]. As for other rheumatic diseases, an active disease before conception is predictive of APO and active disease throughout pregnancy [35]. Disease onset during pregnancy or the postpartum period has also been reported in 3.7–9% of patients [36,37]. Prospective studies and larger cohorts are needed to assess if pregnancy can be a trigger of myositis.

VASCULITIS

Systemic vasculitis are a wide group of autoimmune diseases that share inflammatory damage of the vessel wall [38]. The incidence of these diseases has a peak after the age of 40 and there is a male predominance, apart from Beçhet disease and Takayasu arteritis, which tend to affect mostly young women. As pregnancy is a prothrombotic state and these diseases have a vascular involvement, special attention should be given to thromboprophylaxis in these women [39].

BEÇHET DISEASE

Beçhet Disease (BD) is a systemic vasculitis that can affect any size and type of vessel characterized by oral and genital ulcers, skin lesions, and ocular involvement. Its onset is frequent during childbearing age. Approximately 30% of patients experience a flare during pregnancy, 60% experience an improvement during pregnancy, and 10% remain stable [38,40].

TAKAYASU ARTERITIS

Takayasu arteritis is a chronic large vessel vasculitis that leads to stenosis and occlusion of arteries in individuals below the age of 40 years. Pregnancy does not seem to influence disease activity, as flares were estimated to occur in 3% of the patients in a systematic review of the literature [38]. Nevertheless, when a flare occurs it can be severe (aortic dissection, stroke). Takayasu arteritis has been proposed as an independent risk factor for the development of aortic dissection in pregnancy [38]. Physiologic adaptive changes of the cardiovascular system may worsen preexisting vascular lesions [40] with consequent higher risk of complications, such as hypertension.

PANARTERITIS NODOSA

Panarteritis nodosa is a chronic granulomatous medium vessel vasculitis. When pregnancy starts during disease remission, outcomes are rather favorable [40]. Data about pregnancies are still limited, mostly from case reports. Disease onset during pregnancy leads to a high death rate and few patients have been reported to survive [38].

SMALL VESSEL VASCULITIS

Small vessel vasculitis (SVV) or ANCA-related vasculitis includes granulomatosis with polyangiitis (GPA), eosinophilic

granulomatosis with polyangiitis (EGPA) and microscopic polyangiitis (MPA). GPA is said to flare in up to 40% of women when pregnancy starts in disease remission. Otherwise GPA was found to flare in 100% of patients with active disease at conception [38]. EGPA has been found to flare in 24% of patients; lethal flares have been described related to cardiac and pulmonary involvement. Data from MPA are scarce. It must be noted that 20% of flares were life threatening [40], so close monitoring is mandatory in these patients. Disease onset during pregnancy has been reported more frequently than in other rheumatic diseases, and such a situation had a poor pregnancy outcome. Larger cohorts will be able to assess whether there is a real association between pregnancy and SVV onset [40].

The disease course during pregnancy may vary on different rheumatic diseases. Among inflammatory arthritis, a majority of RA and JIA patients improve spontaneously during pregnancy, even though less frequently than described in the past [2]. Pregnancy has no major effect on disease activity in axSpA, but treatment is often necessary [9]. PsA seems to improve but few studies are still available [9]. In SLE, the flare rate during pregnancy may be different from study to study and it may reflect the severity of different disease subsets and different management during pregnancy. Data on other CTD courses during pregnancy is limited and often inconclusive. Complications during pregnancy are associated with active disease and organ involvement at conception. A special consideration should be given to APS because pregnancy complications are a disease hallmark. Pregnancy does not seem to worsen the activity of systemic vasculitis when started during remission, but a disease flare during pregnancy can lead to severe complications [39].

Despite the fact that the disease course during pregnancy changes from one condition to another, it is now well-known that maternal flare risk depends on disease activity before conception and active disease during pregnancy is associated with APO [1]. It is increasingly recognized that the risks of pregnancy associated with rheumatic diseases can be minimized if conception is planned during a period of sustained remission or minimally active disease. For this reason, it is important to perform a preconception counseling to evaluate maternal disease activity and to adjust treatment [39]. Today, we know that most of the disease-modifying anti-rheumatic drugs are safe during pregnancy and lactation [1]. Therefore, it is strongly recommended to maintain the treatment during pregnancy, as the discontinuation of the ongoing treatment at positive pregnancy index has been associated with maternal disease flares during pregnancy and poorer pregnancy outcomes [5]. Except for RA and SLE, studies of most other conditions are influenced by small sample size, different study designs, and population, lack of objective measures.

CONCLUSIONS

Further prospective studies with large sample sizes, such as nationwide registers, are needed to enhance our knowledge

on the interaction between rheumatic diseases and pregnancy. A flare during pregnancy may be the key difference between an uncomplicated pregnancy and a pregnancy with poor maternal and/or fetal outcomes. Therefore, knowledge about the risk factors leads to the best treatment strategies to reduce flares and obstetric complications in pregnant women with rheumatic diseases.

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"There is always a time for gratitude and new beginnings"

J. Robert Moskin (b. 1923), American historian, writer, and editor