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Disease activity assessment of rheumatic diseases during pregnancy: a comprehensive review of indices used in clinical studies

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ABSTRACT

Pregnancy requires a special management in women with inflammatory rheumatic diseases (RDs), with the aim of controlling maternal disease activity and avoiding fetal complications. Despite the heterogeneous course of RDs during pregnancy, their impact on pregnancy largely relates to the extent of active inflammation at the time of conception. Therefore, accurate evaluation of disease activity is crucial for the best management of pregnant patients. Nevertheless, there are limitations in using conventional measures of disease activity in pregnancy, as some items included in these instruments can be biased by symptoms or by physiological changes related to pregnancy and the pregnancy itself may influence laboratory parameters used to assess disease activity. This article aims to summarize the current literature about the available instruments to measure disease activity

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during pregnancy in RDs. Systemic lupus erythematosus is the only disease with instruments that have been modified to account for several adaptations which might interfere with the attribution of signs or symptoms to disease activity during pregnancy. No modified-pregnancy indices exist for women affected by other RDs, but standard indices have been applied to pregnant patients.

The current body of knowledge shows that the physiologic changes that occur during pregnancy need to be either adapted from existing instruments or developed to improve the management of pregnant women with RDs. Standardized instruments to assess disease activity during pregnancy would be helpful not only for clinical practice but also for research purposes.

1. Introduction

Rheumatic diseases (RDs) often affect women during childbearing age. Planning a family is now a reality for these women, thanks to earlier diagnosis and improved management of RDs. Pregnancy is a delicate period that needs a special management to control the maternal disease and to avoid complications for both the mother and the fetus. The management of RDs during pregnancy should aim at minimizing the effects of maternal disease on pregnancy outcome.

Rheumatoid arthritis (RA) and chronic inflammatory arthritis, such as polyarticular juvenile idiopathic arthritis (JIA), tend to improve spontaneously during pregnancy in the majority of patients [1], even though less frequently than described in the past [2]. Spondyloarthritis (SpA) tend to be stable or to get worse during pregnancy, even though the available literature is scarce [1]. Systemic lupus erythematosus (SLE) can flare up to 50% of pregnancies, including a major organ involvement in nearly 25% of the cases [1]. The effect of other connective tissue diseases (CTD) on pregnancy or *vice versa* has been less investigated. A special consideration should be given to anti-phospholipid syndrome (APS) because one of its main clinical manifestations are pregnancy complications. Pregnancy does not seem to worsen the activity of systemic vasculitis, but a disease flare during pregnancy can lead to severe complications [3].

Active disease or flares during pregnancy can negatively impact fetal health and pregnancy outcome [4]. Therefore, accurate evaluation of disease activity is crucial for the best management of these patients. However, there are limitations in using conventional measures of disease activity in pregnancy, as some items from these instruments can be biased by symptoms or by physiological changes related to pregnancy and pregnancy itself may influence laboratory parameters [5]. In particular, some laboratory investigations have to be interpreted with caution: mild anemia, mild thrombocytopenia, proteinuria, and increased erythrocyte sedimentation rate (ESR) are common during pregnancy. Complement levels become less informative with the increase in levels during normal pregnancy and renal function should be interpreted considering the physiological increased plasma volume and glomerular filtration rate. Pregnancy can cause skin manifestations, mild knee effusion and low back pain that can interfere with the evaluation of disease activity.

Most of the studies on this subject have focused on SLE and RA. However, different instruments and definitions of remission or flares were used, making it difficult to compare different cohorts. It clearly emerges that valid measures of disease activity during gestation are of pivotal importance. The paucity of documentation and the lack of standardization make this a focal point to review.

The aim of this narrative review is to summarize the scientific literature available on instruments to assess disease activity during pregnancy in different RDs.

2. Measurement of disease activity in pregnant patients with rheumatic diseases

2.1. Rheumatoid arthritis

Women have a three-fold higher risk of developing RA than men, and the number of patients experiencing a pregnancy has significantly expanded over the last two decades, polarizing a growing attention on reproductive health matters [6]. An active disease during pregnancy has been clearly demonstrated to increase the risk of preterm delivery and placental insufficiency leading to low birth weight, while the association of pre-eclampsia (PE) and gestational hypertension with active RA is still debated [7,8]. Hench, back in 1938, was the first author to describe the ameliorating effects of pregnancy on RA [9]. This observation was confirmed by following early studies, all concordant in reporting high rates of disease improvement or remission during gestation (Table 1). Unfortunately, these findings were to be downsized in forthcoming years: it is now well ascertained that RA improves during pregnancy, but to a much lower extent than what was believed in pioneering times. The explanation of such striking difference should be ascribed to the fact that early reports had a retrospective design, assessed disease activity heterogeneously, often relying on the amelioration of symptoms reported by patients. Furthermore, in modern rheumatology an optimal disease control can be reached, thus limiting the ameliorative potential of pregnancy. However, no modified pregnancy disease activity index has been developed in RA. Studies in the field have investigated a number of different parameters: ESR, C reactive protein (CRP), clinical examination, self-reported activity measures, or clinimetric indices commonly used in clinical practice including visual assessment scale (VAS), disease activity score (DAS28), health assessment questionnaire (HAQ), short-form 36 (SF-36) [10]. As mentioned above, pregnancy itself can potentially affect several of these parameters: ESR physiologically increases during gestation, while fatigue, anemia and arthralgias are quite common in pregnancy, potentially influencing VAS and global health (GH) [11]. Moreover, physical changes related to pregnancy, such as weight gain, can impact functional abilities included in HAQ [11]. Few studies have assessed the performance of the common clinimetric indices during gestation. To note, many studies are from the Dutch Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA) cohort, which might cause a bias for duplication of data (Table 1). De Man demonstrated that a healthy pregnancy can influence different components of DAS28, with average score increase of 0.22 for GH, 1.1 for ESR, and 0.25 for CRP. Consequently, DAS28-CRP3, excluding the patient GH assessment, emerged as the best tool to assess disease activity in pregnant RA women [11]. More recently, the patient-administered Rheumatoid Arthritis Disease Activity Index (RADAI) has been shown to correlate with DAS28-CRP3 in 32 pregnant RA patients, suggesting that this simple and fast questionnaire could represent a good option to assess disease activity in pregnant RA women, at least outside a rheumatology clinic [12]. Interestingly, in 17 of these 32 patients, Clinical Disease Activity Index (CDAI) was also performed: it correlated well with both DAS28-CRP3 and RADAI, suggesting that CDAI could be useful even during pregnancy [12]. Conversely, Simple Disease Activity Index (SDAI) has never been validated in this setting and is not currently used in RA pregnant women. At present DAS28-CRP3 is addressed as the best clinimetric index to evaluate disease activity in pregnant RA patients, but further studies are needed to define if an *ad hoc* modified activity score could perform better.

Table 1
Clinimetric indices used in RA pregnant women.

Author [Ref]	Year	Study design	N of pregnancies	Evaluation of disease activity	Definition of improvement	Definition of remission	Definition of flare	Rate of disease improvement	Rate of remission	Rate of flares	Rate of post-partum flares
Hench [9]	1938	R	34	Self-reported joint symptoms	/	/	/	90%	/	/	90%
Oka [105]	1953	R	114	Self-reported joint and general symptoms	/	/	/	77%	/	/	83.3%
Hargreaves [106]	1958	R	11	Clinical notes	/	/	/	91%	/	0%	91%
Smith [107]	1960	R	11	Clinical notes	/	/	/	27.3%	45.5%	27.3%	81.8%
Morris [108]	1969	R	19	Clinical notes	/	/	/	21%	/	15.8%	/
Unger [109]	1983	P	14	- Mild disease activity: 1–3 active joints - Moderate disease activity: > 4 active joints	/	Camp index < 6 Camp index < 16	/	/	71%	2%	/
Østensen [110]	1983	R	49	- Duration of morning stiffness (score 1–4) - Functional capacity (score 1–4) - Drugs needed to control disease (score 1–4)	Reduction in the score	Score < 5	/	75%	/	/	62%
Østensen [111]	1983	P	12	- Duration of morning stiffness (score 1–4) - Ritchie articular index (score 1–4) - Number of swollen joints (score 1–4) - Grip strength (score 1–4) - Functional class (score 1–4) - Performance of activities of daily living (score 1–4)	Reduction in the score	Score < 8	/	/	83%	16.6%	91.6%
Nelson [112]	1993	R/P	57	- Reported joint symptoms - Use of medications - Physical examination	Reduction of arthritis medication, no > 15 min of morning stiffness, improvement of joint tenderness, no joint swelling in the III trimester	No use of arthritis medication, no > 15 min of morning stiffness, no joint tenderness, no joint swelling	/	21%	38.6%	/	/
Quinn [113]	1993	P	24	Arthritis Impact Measurement Scale (AIMS)	Reduction in AIMS score	/	/	/	88%		79%
van der Horst-Bruinsma [114]	1998	R	33	- Self-reported joint symptoms - Review of clinical records - Drugs	/	/	/	82%	18%	/	/

(*continued on next page*)

Table 1 (*continued*)

Author [Ref]	Year	Study design	N of pregnancies	Evaluation of disease activity	Definition of improvement	Definition of remission	Definition of flare	Rate of disease improvement	Rate of remission	Rate of flares	Rate of post-partum flares
Barrett [115]	2000	P	137	- VAS of swollen joints - VAS of tender joints	/	/	/	/	/	/	- 65.6%: worsening of VAS of swollen joints - 76.6%: worsening of VAS of tender joints
Brennan [116]	2000	P	140	- 6-point scale calculated from a standardized questionnaire - Clinical examination by a nurse	Changes in self-reported pain and swelling	No swollen joint and no treatment	/	44.3%: improved in joint swelling 49.3%: improved in joint pain	/	/	/
Østensen [18]	2004	P	10	- RADAI - 44 joint count - HAQ	- Decrease in RADAI of 1.0–1.5 - Decrease in HAQ of 0.17	- Morning stiffness < 15 min - No soft tissue swelling in joints or tendon sheaths - No joint tenderness or pain on motion - No need for drug treatment	- Increase in RADAI of 1.0–1.5 - Increase in HAQ of 0.17	40%	30%	/	60%
Østensen [117]	2005	P	34	- RADAI - Tender joint count - Swollen joint count - PGA	Decrease in PGA > 20	PGA of 0	Increase in PGA < 20	50%	/	/	/
Forger [118]	2005	P	10	- RADAI - SF-36				70%	/	/	60%
De Man* [11]	2007	P	30	- DAS28-ESR4 - DAS28-ESR3 - DAS28-CRP4 - DAS28-CRP3	/	DAS28 < 2.6	/	/	- DAS28-ESR4: 11% - DAS28-ESR3: 0% - DAS28-CRP4: 17% - DAS28-CRP3: 23%	/	/
De Man* [2]	2008	P	84	DAS28-CRP3	EULAR response criteria	DAS28 < 2.6	Reversed EULAR response criteria	48% in women with moderate disease activity at the beginning of pregnancy. Stable disease activity in women with low disease activity.	/	/	39%
De Man* [7]	2009	P	152	DAS28-CRP3	/	/	/	/	/	/	/
De Man* [119]	2010	P	118	DAS28-CRP3	EULAR response criteria	/	Reversed EULAR response criteria	34%	/	/	42%
Zrour [120]	2010	P	13	- DAS28 - HAQ - EULAR tender joint number - EULAR swollen joint number	Decrease of morning stiffness and of the number of tender or swollen joints	Disappearance of symptoms despite treatment withdrawal, morning stiffness < 15 min, no tender or swollen joints	Increase of disease activity signs	/	/	/	92%
Forger [121]	2012	P	22	DAS28-CRP3	/	/	/	/	/	/	/

(*continued on next page*)

Table 1 (*continued*)

Author [Ref]	Year	Study design	N of pregnancies	Evaluation of disease activity	Definition of improvement	Definition of remission	Definition of flare	Rate of disease improvement	Rate of remission	Rate of flares	Rate of post-partum flares
Quax* [122]	2012	P	147	DAS28-CRP3	EULAR response criteria	/	Reversed EULAR response criteria	45.1%	/	/	73.6%
Bondt* [123]	2013	P	251	DAS28-CRP3	EULAR response criteria	/	Reversed EULAR response criteria	47.1%	/	/	60%
Weix [124]	2013	P		DAS28CRP	/	DAS28-CRP3 < 2.6	/	/	60%	/	/
De Steenwinkel * [125]	2014	P	/	DAS28-CRP3	/	/	/	/	/	/	/
De Steenwinkel * [126]	2014	P	255	DAS28-CRP3	/	/	/	/	/	/	/
Langen [127]	2014	R	46	- Joint tenderness - Joint stiffness - Joint swelling	/	/	Necessity to intensify treatments. Need for hospitalization for musculoskeletal complaints.	/	/	53.3%	60%
Atta [128]	2016	P	47	DAS28-CRP3	/	/	/	/	/	/	/
Brouwer* [129]	2015	P	162	DAS28-CRP3	/	/	Reversed EULAR response criteria	/	/	/	/
Ince-Askan* [130]	2016	P	27	DAS28-CRP3	Decrease in DAS28 > 0.6	/	Increase in DAS28 > 0.6	37%	/	22.2%	63%
Tham [131]	2016	P	28	DAS28-CRP3	/	DAS28-CRP3 < 2.6	/	/	/	/	/
Van den Brandt [14]	2017	P	75	DAS28-CRP3	/	/	Increase of DAS28-CRP > 0.6	/	/	/	/
Ince-Askan* [132]	2017	P	190	DAS28-CRP3	/	DAS28-CRP3 < 2.6	/	/	30.5%	/	/
Bermas BL [12]	2017	P	30	DAS28-CRP3 CDAI RADAI	/	/	/	/	/	/	/
De Steenwinkel * [133]	2017	P	105	DAS28-CRP3	/	/	/	/	/	/	/
Bondt* [134]	2018	P	152	DAS28-CRP3	EULAR response criteria	/	Reversed EULAR response criteria	/	/	/	/
Zbinden [19]	2018	P	96	DAS28-CRP3	/	/	/	/	/	/	/

Legend - CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; EULAR: European League Against Rheumatism; HAQ: Health Assessment Questionnaire Disability Index; P: prospective; PGA: Physician Global Assessment; R: retrospective; RADAI: Rheumatoid Arthritis Disease Activity Index; SF-36: 36-Item Short Form Health Survey; VAS: Visual Analog Scale.

* Dutch Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA) Study.

2.2. Spondyloarthritis

SpA are a group of disorders including psoriatic arthritis (PsA) and ankylosing spondylitis (AS) that share similar pathogenic and clinical features [13]. During pregnancy, patients with SpA can experience either an active disease or a stable/reduced disease activity. Recent studies in small cohorts of SpA patients showed a disease flare during pregnancy in 25% of patients affected by axial SpA [14] while a reduced disease activity was demonstrated in 70% of AS patients [15]. Several different instruments have been proposed to measure diseases activity in SpA, as unidimensional (focused on joint activity) and as multidimensional (combining different domains) clinimetric indices [16,17]. However, concerning pregnancy and childbearing, no modified indices for disease activity exist for SpA. Standard clinimetric indices were used to measure disease activity during pregnancy in patients affected by AS and PsA. The Bath Ankylosing Spondylitis Activity Index (BASDAI) was used in a prospective study in 9 pregnant women with AS. Higher disease activity scores during the second trimester and a mitigation of symptoms in the third trimester were observed. A good to moderate correlation between most clinical measurements were shown, even if functional indices (including bending), measures of pain and fatigue might be confounded by physiological changes of late pregnancy [18].

Two retrospective studies [14,15] and one prospective study [19] used the Ankylosing Spondylitis Disease Activity Score (ASDAS) during pregnancy in 61 axial SpA patients and 20 AS pregnant women. ASDAS was used to evaluate disease activity, flares and treatment response during pregnancy. Lui and colleagues also evaluated night pain and morning stiffness in 19 AS pregnant women; an improvement in these parameters was registered in the first trimester while a worsening was detected in the third trimester likely secondary to biomechanical loading [20]. Concerning PsA, no robust data are available due to the low sample size. However, women with psoriasis may encounter new-onset psoriasis in addition to flares in 45% of the patients during pregnancy, and in 65% up to 6 weeks postpartum; the clinimetric index used was the Psoriasis Area and Severity Index (PASI) [21]. In a recent study on 29 PsA women with 42 pregnancies, a worsening of joint and skin activity was found in 31.7% and 42.9% respectively, during pregnancy and in the first year after delivery. Joint disease was measured as the number of inflamed joints and based on the definition of the Minimal Disease Activity (MDA) [22]. No modified-pregnancy indices exist for women affected by SpA. Of note, several symptoms such as lumbar night pain, morning stiffness and fatigue could be influenced by pregnancy itself; therefore, disease activity might be overestimated [18]. Moreover, the course of the SpA during pregnancy is extremely variable with some data reporting an improvement and others a worsening of the disease. In the field of SpA, several missing data emerged. Composite clinimetric indices were never tested in SpA pregnant women neither the impact on quality of life, by means of SF-36 or HAQ-SpA, were evaluated in this population.

2.3. Juvenile idiopathic arthritis

JIA comprises a heterogeneous group of diseases, mainly characterized by the presence of inflammatory arthritis with an onset before 16 years of age [23]. JIA is more frequent in females than in males and in more than one third of patients the disease can persist in adulthood [23]. The dramatic changes in the prognosis resulting from the introduction of biological agents have increased the number of JIA female patients experiencing a pregnancy [24]. However, very few studies have assessed disease activity during gestation in JIA and no validated clinimetric index is currently available. Ursin has recently described the impact of pregnancy on disease activity in 114 women with JIA, using DAS28-CRP3, modified HAQ (MHAQ) and SF-36 [25]. Given the absence of validated clinimetric scores for disease activity of JIA in pregnancy, DAS28-CRP3 could represent a reliable activity index in a disease, very similar to RA.

2.4. Systemic lupus erythematosus

In SLE patients, pregnancy is considered at high-risk and it is associated with an increased risk of flares, particularly in patients with active disease at the time of conception [26]. Women with previous lupus nephritis should be carefully managed for the risk of flare during pregnancy and/or the onset of PE [27]. Therefore, a strict assessment and a tight control of disease activity before and throughout pregnancy is crucial; however, physiological changes in pregnancy may mimic a lupus flare (e.g. constitutional symptoms, non-inflammatory joint pain, skin rash, alopecia), as well as, laboratory changes (e.g. anemia, thrombocytopenia, proteinuria, increase of ESR) [26]. There is increasing interest in this topic, as the health conditions of children born to mothers with SLE have been claimed to be possibly associated with maternal disease activity during pregnancy [28] or to the transplacental passage of maternal autoantibodies as in the case of anti-Ro/SSA antibodies [29].

Established lupus activity scales, such as the Lupus Activity Index (LAI), the SLE Disease Activity Index (SLEDAI) and the Systemic Lupus Activity Measure (SLAM), were originally validated in SLE patients excluding pregnant women. In order to reduce confounding features from physiological pregnancy and SLE exacerbations, in 1999 the members of the Systemic Lupus International Cooperating Clinics proposed three modified-pregnancy scores: the SLE-Pregnancy Disease Activity Index (SLEPDAI), the LAI in Pregnancy (LAI–P) and the modified SLAM (m-SLAM) [5]. More recently, two other pregnancy-adapted scores have been introduced, the modified-European consensus lupus activity measurement (m-ECLAM) [30] and the British Isles Lupus Assessment Group-2004 for pregnancy (BILAG2004-P) [31]. The main features of each index are summarized in Table 2.

In the LAI–P, proposed by Khamashta and Ruiz-Irastorza [5], the VAS from the original version was replaced with a graded scale. Some items in the original LAI were excluded (e.g. patient global assessment (PGA) and fatigue) to avoid pregnancy related symptoms to be scored as disease activity and other more objective terms, such as “vasculitis,” “fever,” or “myositis,” were added [32]. The relative weight of every item has also been modified. Manifestations related to APS, such as cerebrovascular accidents or thrombocytopenia, were not scored in LAI-P in patients with antiphospholipid antibodies (aPL) unless other signs of lupus activity were present. The LAI-P includes 4 groups: Group 1 (fever, rash, arthritis and serositis); Group 2 (neurologic, renal, lung, hematologic, vasculitis and myositis); Group 3 (prednisone/NSAIDs/hydroxychloroquine (HCQ) and immunosuppressants) and Group 4 (proteinuria, anti-DNA, and C3/C4). The LAI–P, validated in 2004 [29], has been recently used to explore the associations between disease activity and medications with offspring birth weight, PE and preterm birth in Swedish pregnant women with SLE [33].

In SLEPDAI, 15 out of the 24 original items of the SELENA-SLEDAI were modified [5]. The 15 items that should be carefully examined before scoring are: seizure, headache, cerebral infarction, cranial nerve disorder, vasculitis, arthritis, hematuria, proteinuria, pyuria, rash, alopecia, pleurisy, low complement levels, thrombocytopenia, and leukopenia. To be considered as a flare of lupus, some pregnancy-related physiological changes must be ruled out, including: 1) PE/eclampsia (E), and Bell's palsy when considering neurologic involvement; 2) the presence of isolated microscopic hematuria, mild proteinuria (< 500 mg/24 h), and/or pyuria (also common in urinary tract or vaginal infections) when considering renal involvement; 3) bland joint effusions, frequent during pregnancy; 4) melasma, transient nonspecific facial blush, palmar erythema, and postpartum alopecia when considering cutaneous involvement; 5) mild resting dyspnea before considering pleurisy; 6) PE/E, HELLP (hemolysis elevated liver enzymes low platelet count) syndrome, incidental thrombocytopenia, abruption placentae, fetal demise, and aPL should be considered when there is hematologic involvement such as thrombocytopenia [5]. SLEPDAI has not been formally validated, although it has been used in three studies,

Table 2
Main features of LAI–P, SLEPDAI, m-SLAM, m-ECLAM and BILAG2004-P.

Features		LAI–P	SLEPDAI	m-SLAM	m-ECLAM	BILAG2004-P
Modified items						
General	Weight loss	NA	NA	**–**	NA	=
	Fatigue	**–**	NA	**r/o FM**	=	NA
	Fever	+	=	=	=	=
	PGA	**–**	NA	NA	NA	NA
Musculoskeletal	Arthritis	=	**c bland knee effusions**	**c bland knee effusions**	=	**r/o bland knee effusion, peripheral edema of pregnancy and mechanical pain**
	Arthralgia	NA	NA	**c bland knee effusions**	=	=
	Myalgia	NA	NA	**r/o FM**	NA	=
	Myositis	+	=	=	=	=
Neurologic	Seizure	**r/o PE/E**	**r/o E**	**r/o E**	=	=
	Psychosis	**r/o PE/E**	=	NA	=	=
	OBS	**r/o PE/E**	=	**r/o PE, E**	=	=
	Visual disturbances	**r/o PE/E**	=	NA	NA	=
	Cranial nerve disorder	**r/o PE/E, not scored d if aPL+**	**r/o Bell's palsy**	NA	NA	=
	Lupus headache	=	**r/o PE/E**	**r/o E**	=	=
	CVA	**not scored if aPL+ unless other signs of lupus activity are present**	**r/o E**	**r/o PE, E**	=	**r/o E**
	Vasculitis	+	**c palmar erythema**	**c palmar erythema**	=	=
Renal	Urinary casts/sediment	=	=	=	=	=
	Hematuria	=	**r/o infection o placental problems**	**r/o placental problems**	=	NA
	Proteinuria	**≥500 mg/day or doubling if previous LN, associated to low levels of complements or increase of anti-dsDNA after r/o PE**	**r/o E**	=	**≥500 mg/day after r/o PE**	**r/o PE, E**
	Pyuria	=	**r/o infection**	**r/o infection**	NA	NA
	Serum Creatinine	=	NA	**c normal decrease during pregnancy**	=	**c normal decrease during pregnancy**
Hematological	Thrombocytopenia	**not scored if aPL+ unless other signs of lupus activity are present**	**r/o PE, HELLP syndrome, incidental thrombocytopenia during pregnancy**	**r/o PE, HELLP syndrome, incidental thrombocytopenia during pregnancy**	=	**r/o PE, HELLP syndrome and APS**
	Neuthophils/Lymphocyte	=	NA	=	NA	**consider normal increase during pregnancy**
	Hematocrit	=	NA	**c hemodiluition**	NA	NA
	Hemolytic anemia	=	NA	NA	=	**r/o HELLP syndrome**
	Non-hemolytic anemia	NA	NA	NA	**–**	**c hemodiluition**
	Lymphocyte count	=	**c normal increase during pregnancy**	**c normal increase during pregnancy**	=	**c normal increase during pregnancy**
Cardiovascular/ Cardiorespiratory	Pericarditis	=	=	=	=	=
	Pleurisy	=	**c hyperventilation due to progesterone and dyspnea due to enlarging uterus**	**c hyperventilation due to progesterone and dyspnea due to enlarging uterus**	=	=
	Hypertension (diastolic)	NA	NA	**r/o PE, E**	NA	**omitted from the renal section**
	Raynaud	NA	NA	=	NA	NA
	Serositis	=	NA	=	=	=
Mucocutaneous	Rash	=	**c chloasma**	**r/o chloasma**	=	**r/o melasma, chloasma**
	Alopecia	NA	**c postpartum alopecia**	**c postpartum alopecia**	NA	**c postpartum alopecia**
	Mucosal Ulcers	NA	=	=	=	=
Gastrointestinal	Abdominal pain	NA	NA	=	=	=
Ophthalmologic	Hemorrhages (retinal, choroidal) or episcleritis	**r/o PE/E, not scored if aPL+**	NA	**r/o PE, E**	NA	=

(*continued on next page*)

Table 2 (*continued*)

Features		LAI–P	SLEPDAI	m-SLAM	m-ECLAM	BILAG2004-P
Laboratory	Complement	=	**c normal increase during pregnancy**	NA	=	**added in renal section**
	anti-dsDNA	=	=	NA	NA	**added in renal section**
	ESR	NA	NA	–	–	NA
Drugs	PDN, NSAIDs, HCQ	=	NA	NA	NA	NA
	Immunosuppressants	=	NA	NA	NA	NA
Response options		**severity scale**	**weighted variables**	**severity scale**	**weighted variables**	**severity scale**
Recall period for items		**2 weeks**	**10 days**	**1 month**	**1–3 month**	**4 weeks**
Scoring		**Group 1(mean)+2 (max)+ 3 (mean)+ 4 (mean)/4**	**sum of all items**	**sum of all items**	**sum of all items**	**Each question is recorded as 0, 1, 2, 3, or 4 and a computer program facilitates scoring from numerical to alphabetical score for each system (grade A–E)**
Final score		**0–2.6**	**0–105**	**0–81**	**0–17.5**	**A-E**
Definition of active disease		**flare: increase of 0.25 from the last evaluation**	**4–11: moderate activity; > 12: severe activity**	**≥7 active disease**	**≥2 active disease**	**A, severe; B, moderate; C, mild stable disease; D, no disease activity; E, no current or previous disease activity**
Validated for the use in pregnancy		**yes**	**no**	**no**	**no**	**no**
Used in studies of pregnant patients		**yes**	**yes**	**no**	**yes**	**no**

Legend: −, eliminated; +, added; = unchanged – as compared to the original version of the index; c, consider; r/o: rule out; aPL: anti-phospholipid antibodies; APS: anti-phospholipid syndrome; BILAG2004: British Isle lupus activity group; CVA: Cerebrovascular accident; E: eclampsia; ESR: erythrocyte sedimentation rate; FM: fibromyalgia; HCQ: Hydroxychloroquine; HELLP: Hemolysis elevated liver enzymes low platelet count; LAI-P: Lupus activity index-pregnancy; LN: lupus nephritis; NA, not applicable; m-SLAM: Modified systemic lupus activity measure; NSAIDs: Nonsteroidal anti-inflammatory drugs; OBS: organic brain syndrome; PDN: prednisone; PE: pre-eclampsia; PGA: physician global assessment; RBC: Red blood cells; SLEPDAI: Systemic lupus erythematosus pregnancy disease activity index; WBC: White blood cells.

two of which were designed to assess the effect of HCQ on SLE exacerbations in pregnant women [34,35] and one more recent evaluating the complement activation as a predictor of adverse pregnancy outcome in patients with SLE [36].

In 1995, a modification of SLAM-R, the m-SLAM, was proposed by Ramsey-Goldman and colleagues [37]. Some items were eliminated from SLAM-R, such as weight loss, ESR, and the *ad hoc* scale for miscellaneous disease manifestations [37]. Several descriptors, such as fatigue, myalgia, arthralgia, gastrointestinal symptoms, lymphadenopathy, hepatosplenomegaly, Raynaud's phenomenon, and hypertension, that are not addressed in the SLEPDAI and LAI–P, are included in the m-SLAM [5].

In two prospective studies published in 2002 [30] and 2004 [38] Doria et al. used a modified version of ECLAM, the m-ECLAM. Three of the original 15 items were changed as follows: 1) proteinuria considered pathological if ≥500 mg/day and after excluding PE; 2) non-hemolytic anemia was not considered due to its high frequency during pregnancy; and 3) ESR was not considered due to its physiological increase during pregnancy [30].

In 2012, the BILAG2004-P index was introduced by Yee and colleagues [31]. The major modification was in the assessment of renal involvement: complement levels (C3 and C4) and anti-dsDNA were added to differentiate proteinuria due to lupus nephritis from PE and hypertension was omitted from the index [31]. Similarly to other indices, the glossary also changed to remind the physician of the confounding items during pregnancy.

In all the above-mentioned indices, modifications were made to address influential items: some were eliminated (e.g. ESR, asthenia) and others were adapted to physiological pregnancy changes (e.g. proteinuria levels), emphasizing the need to differentiate those changes from pregnancy comorbidities (e.g. PE/E). The scoring of each index is calculated in the same way as the original version, except for the LAI–P, in which the weighted score given to each item has been modified. Even though many attempts have been made to develop a pregnancy-specific disease activity index that can be reliable and valid in measuring disease activity, the clinical judgment of an experienced physician remains the gold standard in the management of pregnant women with SLE. As recently recommended [39], these women should be frequently monitored (every 2 to 8 weeks) and during each visit the PGA in conjunction with at least one of the activity tools and pregnancy-specific SLE activity indices (such as SLEPDAI, LAI–P, BILAG 2004-P) should be applied.

2.5. Anti-phospholipid syndrome

The assessment of disease activity in APS is different compared to other RDs. As already mentioned, APS can present thrombosis and/or pregnancy complications, as main clinical manifestations. No clinimetric indices exist for APS, but a scoring system has been developed to predict the risk of thrombosis (either first or recurrent) and pregnancy morbidity [40]. Studies in pregnant women with APS, used the occurrence or recurrent of arterial or venous thrombosis, pregnancy complications and non-criteria APS manifestations to assess the disease course during pregnancy [41,42].

2.6. Other connective tissue diseases

2.6.1. Undifferentiated connective tissue disease

Undifferentiated connective tissue disease (UCTD) is a rheumatic disease with combination of signs and symptoms of connective tissue disease, that does not fulfill criteria for a major CTD. Pregnancies in UCTD have been described and many studies have investigated pregnancy outcome [43]. The evaluation of disease course during pregnancy has also been assessed. Mosca et al. studied a population of 20 UCTD patients during their 25 pregnancies to investigate disease flare during pregnancy, pregnancy course and to determinate if pregnancy could be a trigger for disease evolution to a defined CTD. Flare in UCTD was defined as a disease activity increase based on physician's assessment and on therapeutic changes [44]. Also, Castellino et al. studied the outcome of 55 pregnancies in 50 UCTD patients followed during pregnancy and 6 months after delivery; maternal outcome was also investigated to detect disease relapse or differentiation into defined CTD comparing the ouctome of pregnant patients with a control-population of 53 non-pregnant UCTD followed for 16 months. Disease flare was based on clinical judgment: new onset or worsening of pre-existing symptoms and/or treatment modifications [45]. So, at present, no validated indices have been proposed to assess disease activity in UCTD patients and clinical judgment still is the gold standard for both pregnant and non-pregnant patients.

2.6.2. Mixed connective tissue diseases

Mixed connective tissue disease (MCTD) is an autoimmune CTD characterized by an overlap syndrome with features of lupus, scleroderma, and poly/dermatomyositis (PM/DM), in patients who carry positivity for anti-U1 ribonucleoprotein (RNP) autoantibodies. Patients may exhibit manifestations of any of the composing diseases during the course of the disease [46].

MCTD primarily affects women during the years of childbearing potential [47]; their fertility rates seem to be similar to adjusted age-matched controls. A small number of MCTD cases showed its onset during pregnancy, and definite MCTD have been reported having flares during gestation: a worsening or new onset of clinical manifestations (e.g. worsening of interstitial lung disease, arthritis) were used to describe a disease flare [48–52]. A study focusing on MCTD pregnancy outcome [53] reported a case of a pregnant patient affected by pulmonary arterial hypertension (PAH). The patient was clinically stable, as monitored by six minutes walking test before and during the pregnancy. To date, no validated indices exist to assess disease activity in pregnant and non-pregnant women with MCTD.

2.6.3. Inflammatory myopathies

DM and PM are autoimmune inflammatory myopathies (IM) characterized by proximal symmetric muscle weakness and, in case of DM, a large variety of skin manifestations [54]. As other autoimmune diseases, they predominantly affect female gender [55]. Since the two peaks of IM onset are in childhood and over the age of 45 years, women in reproductive age group are uncommonly affected [54]. Indeed, the proportion of IM onset from 25 to 34 years is estimated to be 4–11% [56]. As a consequence, pregnancies in patients affected with IM are rare.

To date, two international collaborative groups, the International Myositis Assessment and Clinical Studies Group (IMACS) and the Paediatric Rheumatology International Trials Organisation (PRINTO), have defined consensus core set measures to assess myositis disease activity and damage in adults and children and have begun to validate and standardize these measures [57,58].

No recommendations on how to assess IM activity and damage during pregnancy have been done, given the small sample size of the few relevant studies. Thus, the optimal assessment of pregnancy outcome and disease activity in IM patients during pregnancy remains elusive.

IM activity has been defined in some studies by the presence of any rash, muscle weakness and elevation of muscle serum enzymes [59]. Cutaneous manifestations included Gottron papules and heliotrope rash, whereas serum muscle enzymes consist in elevation of creatine-kinase (CK) and/or lactate dehydrogenase (LDH) [60].

A recent study [60] assessed disease activity in pregnant patients by performing both the UK Medical research council system scale (0–5) and the manual muscle strength testing (MMT).

Therefore, the clinimetric indices for IM should be further investigated during pregnancy.

2.6.4. Sjögren's syndrome

Sjögren's syndrome (SS) is an autoimmune systemic disease characterized by dysfunction of exocrine glands and possible multiorgan involvement. Disease activity indices have been created to evaluate two different aspects of the disease: patient's symptoms and systemic activity. Different indices were proposed in the past to assess disease activity but currently no indices have been modified and validated for pregnant SS patients. Many studies have investigated the interaction between SS and pregnancy, but they all focused on pregnancy outcome [61,62]. Only one study by Priori et al. investigated maternal disease during pregnancy and one year post-partum. In this study, no disease activity index was used to assess disease, but flares were defined as the onset or worsening of symptoms leading to therapeutic changes [63].

2.6.5. Systemic sclerosis

Systemic sclerosis (SSc) is a really unpredictable disease. Even if studies published during the last years demonstrated that the majority of women with SSc do not undergo significant modifications of disease activity during pregnancy, neither have worsening of symptoms after delivery [49,64–66], there is a risk of worsening of the disease for some SSc women who have organ involvement such as lungs, heart, and kidneys [66]. Thus, a close monitoring of internal organs and skin involvement, blood pressure and monthly blood tests is mandatory. Until today, there are no validated indices to analyze disease activity, severity and outcome during pregnancy, so that all the studies conducted till now just considered disease progression as changes in organ involvement [64,65,67,68]. Indeed, the definition of disease activity in SSc pregnancy cannot be done using a single variable and the disease activity indices proposed in the literature (the European Scleroderma Study Group (EScSG) activity index, the 12-point DAI, EUSTAR activity index, and the Combined Response Index for Systemic Sclerosis (CRISS)) are preliminary or provisional, not fully validated and not used in studies on pregnancy [69–71]. In the IMPRESS 1 study, a Medsger severity score > 2 in at least 1 item and changes in organ involvements and laboratory exams were used to assess the maternal outcomes in pregnant SSc women [65].

2.7. Systemic vasculitis

Most of the literature focuses on pregnancies in women with Behçet disease (BD) and Takayasu arteritis (TA) because of the earlier median age of onset, however, cases of pregnancy during antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) have also been reported in the literature.

AAV are small-vessel, necrotizing vasculitis primarily affecting the respiratory tract, lungs, kidney, and peripheral nervous system [72]. At present, there is no specific clinical instrument to assess AAV disease activity during pregnancy. In the majority of the studies performed in AAV pregnant patients, disease activity was scored using the Birmingham Vasculitis Activity Score (BVAS) [73] whilst damage due to vasculitis was scored by the Vasculitis Damage Index (VDI) [74]; furthermore, most studies collected the characteristics of the patients (age, type of AAV, organ involvement, ANCA status, ongoing and previous treatment), maternal outcomes (renal function, arterial hypertension, PE), fetal and neonatal outcomes (fetal growth restriction (FGR), prematurity, birth weight, perinatal mortality), type of delivery [75–83]. In the majority of reported cases, women with AAV in remission had a favorable maternal and neonatal outcome with quiescent disease or

Table 3
Disease activity indices used in clinical studies involving pregnant women with Rheumatic diseases.

Rheumatic diseases	Modified pregnancy indices	Standard indices used in studies during pregnancy	Other outcome measures used in studies during pregnancy
RA	–	DAS28-CRP3; RADAI; DAS28-ESR or CRP4; CDAI	Self-reported joints; morning stiffness; Reported joint symptoms and/or treatment modification
AS	–	BASDAI; ASDAS	–
PsA	–	ASDAS; PASI; MDA	Worsening of joint activity and worsening of skin activity (Physician's Judgment)
JIA	–	DAS28-CRP3	–
SLE	LAI-P; SLEPDAI; m-SLAM; m-ECLAM; BILAG2004-P	SLEDAI; PGA	Clinical and laboratory assessment and/or treatment modification (Physicians Judgment)
APS	–	–	–
UCTD	–	–	Worsening or new onset of clinical manifestations and/or treatment modification (Physician's Judgment)
MTCD	–	–	Worsening or new onset of clinical manifestations and/or treatment modification (Physician's Judgment)
DM	–	UK medical research council system scale; MMT	Cutaneous manifestations (Gottron's papules, heliotrope rash) (Physician's Judgment) and elevated muscle enzymes levels (CK, LDH)
PM	–	UK medical research council system scale; MMT	–
SS	–	–	Worsening or new onset of clinical manifestations and/or treatment modification (Physician's Judgment)
SSc	–	Medsger severity score > 2 (in at least 1 item and changes in organ involvement)	–
AAV	–	BVAS; VDI	Typical complications: respiratory, cutaneous, articular, renal
TakA	–	Kerr/NIH index	Two new-onset or worsening items in the previous 3 months
BD	–	–	Onset of new clinical manifestations or increased frequency of symptoms requiring treatment changes (Physician's Judgment)

Legend- A/V: arterial/venous; AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; APS: antiphospholipid syndrome; AS: ankylosing spondylitis; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Activity Index; BD: Behçet disease; BILAG2004-P: British Isles Lupus Assessment Group-2004 for pregnancy; BVAS: Birmingham Vasculitis Activity Score; CDAI: clinical disease activity index; CK: creatine kinase; DAS28-CRP3: disease activity score 28 joints count-C reactive protein; DAS28-ESR: disease activity score 28 joints count-erythrocyte sedimentation rate; JIA: juvenile idiopathic arthritis; LAI–P: Lupus Activity Index in Pregnancy; LDH: lactate dehydrogenase; m-ECLAM: modified-European consensus lupus activity measurement; m-SLAM: modified Systemic Lupus Activity Measure; MDA: Minimal Disease Activity; NIH: National Institutes of Health; PASI: Psoriasis Area and Severity index; PGA: Patients Global Assessment; PsA: psoriatic arthritis; RA: rheumatic arthritis; RADAI: rheumatoid arthritis disease activity index; SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index; SLEPDAI: SLE-Pregnancy Disease Activity Index; SS: Sjögren syndrome; SSc: systemic sclerosis; TakA: Takayasu arteritis; UCTD: undifferentiated connective tissue disease; UK: United Kingdom; MMT: manual muscle strength testing; VDI: Vasculitis Damage Index.

only minor glucocorticoids-dose adjustment; conversely, outcomes were poorer when pregnancies were conceived during active disease or when AAV started during pregnancy [3,75–86]. The most frequent complications were respiratory, cutaneous, articular and renal flares, arterial hypertension, PE, prematurity [3,75–86]. By using BVAS during pregnancy, great attention should be paid to the evaluation of renal, central nervous system and constitutional symptoms that can be confounded by physiological (e.g. proteinuria) or pathological changes (e.g. PE). The item “ischemic abdominal pain” deserves a special mention because it can mimic the abdominal pain during PE.

TA is a large vessel vasculitis primarily affecting aorta and its major branches [87]. At present, a validated clinical instrument to assess TA disease activity in pregnancy does not exist. Some studies in pregnant TA patients used the Kerr/NIH index [88,89] that assesses four items: constitutional manifestations, raised ESR, manifestations of vascular ischemia, angiographic features indicative of vasculitis: disease is defined as active in case of at least two new or worsened items in the previous three months. Nevertheless, items such as ESR and musculoskeletal symptoms can be influenced by pregnancy, so they should be interpreted with caution. Furthermore, most of the studies [3,84,88–93] took into account the general characteristics of the subjects (age, type of arterial involvement, parity, previous obstetric complications), maternal outcomes (glucocorticoid dose increase, CRP and ESR, arterial hypertension, PE, renal and cardiac failure, cardiovascular events), fetal and neonatal outcomes (FGR, prematurity, birth weight, perinatal mortality, Apgar score at 5 min) [3,84,88–95].

Pregnancy does not seem to affect disease activity in TA patients [80], nevertheless, maternal complications such as sustained hypertension, PE, congestive heart failure and cerebrovascular accidents are not uncommon [3,84,88–96].

BD is a multisystemic disorder of unknown etiology characterized by mucocutaneous, ocular, vascular, and central nervous system manifestations [97]. No validated indices assessing BD disease activity in pregnancy are currently available. Disease flares were usually defined as the onset of new symptoms or increased frequency of symptoms requiring treatment changes during pregnancy. Studies on BD pregnancies also evaluated patient's characteristics (age, organ involvement, ongoing and previous treatment), maternal outcomes (arterial hypertension, PE, glucocorticoid dose increase), and fetal/neonatal outcomes (prematurity, low birth weight, perinatal mortality, neonatal intensive care unit admission) [3,84,97]. Pregnancy does not seem to affect disease activity; only around one third of reported cases experiences relapse, primarily with mucocutaneous and ocular manifestations [85,98–100]. In the majority of reported cases, women with BD had pregnancy outcomes similar to those seen in general population even though complications as preterm birth, pregnancy loss, and thrombotic events during pregnancy and puerperium have also been reported [101–104].

3. Conclusions

The physiologic and pathological changes that occur during pregnancy need to be reflected in existing instruments for non-pregnant patient with RDs (Table 3).

To date, SLE is the only disease with modified-pregnancy indices. Five commonly utilized instruments have been modified to account for several adaptations which might confound the attribution of signs or symptoms to disease activity: SLEPDAI, LAI–P, m-SLAM, m-ECLAM and BILAG2004-P.

No modified-pregnancy indices exist for women affected by other RDs. In RA, JIA, SpA and Systemic Vasculitis standard validated indices have been used to assess disease activity in pregnant woman. The DAS28-CRP3 resulted as the best instrument to evaluate disease activity in pregnant RA patients. In other RDs without a validated clinimetric index to assess disease activity, such as SS, MCTD, UCTD, and SSc, studies in pregnant women are scarce and the evaluation of disease activity is still based on the physician's judgment.

Therefore, there is a need to develop modified-pregnancy clinimetric indices to ensure continuity of assessments when RDs patients become pregnant in long-term longitudinal studies. Furthermore, consistent use of a standardized and validated disease activity outcome measure in the assessment of pregnant RDs patients may help address the scarce and, sometimes, conflicting reports of the effects of pregnancy on exacerbation of RDs.

The elaboration and standardization of measure to assess disease activity in pregnant women with RDs will enable us to improve the accuracy of advice to women during pregnancy and to develop better management protocols.

Conflict of interest

All authors have no conflict of interest.

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