UNIVERSITÉ DE LILLE

FACULTÉ DE MÉDECINE HENRI WAREMBOURG

Année : 2023

THÈSE POUR LE DIPLÔME D'ÉTAT

DE DOCTEUR EN MÉDECINE

Effet du post partum sur les patientes atteintes de rhumatismes inflammatoires chroniques

Présentée et soutenue publiquement le 19 juin 2023 à 18h
au Pôle Recherche

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REMERCIEMENTS

ABREVIATIONS

ACR	*American college of rheumatology*
ADA	*Adalimumab*
bDMARD	*Biological Disease-Modifying AntiRheumatic Drug*
BHPR	*British health professionals in rheumatology*
BSR	*The British society rheumatology*
CNGOF	*Collège National des Gynécologues et Obstétriciens Français*
CRP	*C-Reactive Protein*
CS	*Cesarian section*
csDMARD	*Conventional synthetic Disease-Modifying AntiRheumatic Drug*
CTZ	*Certolizumab Pegol*
DAS-28	*Disease Activity Score 28*
ESR	*Erythrocyte sedimentation rate*
ETN	*Etanercept*
EULAR	*European Alliance of Associations for Rheumatology*
GOL	*Golimumab*
INF	*Infliximab*
IRD	*Inflammatory rheumatic diseases*
MTX	*Methotrexate*
NSAIDs	*Non-steroidal anti-inflammatory drug*
PP	*Postpartum*
WHO	*World Health Organization*
PARA	*Pregnancy-induced Amelioration of Rheumatoid Arthritis*
preCARA	*Preconceptional Counselling in Active Rheumatoid Arthritis*
RA	*Rheumatoid arthritis*
RTX	*Rituximab*

SFR	*Société française de rhumatologie*
SpA	*Spondylarthritis*
TNF	*Tumor Necrosis Factor*
tsDMARD	*Targeted synthetic Disease-Modifying AntiRheumatic Drug*

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I. Introduction Générale

La polyarthrite rhumatoïde (PR) et la spondyloarthrite (SpA) font partie des rhumatismes inflammatoires les plus fréquents. Leur prévalence chez les femmes est d'environ 0,47 % à 0,66 % (1) et 0,5 % (2) respectivement.

La première étude concernant l'effet de la grossesse sur la PR a été publiée dans les années 1930 (3). Une rémission de celle-ci était classiquement décrite pendant la grossesse puis un rebond d'activité pendant la période du post-partum (PP) (4). Cependant, des études plus récentes basées sur des cohortes plus importantes ont trouvé des taux de rémission plus faibles que ceux décrits précédemment (5,6)

La littérature est encore plus limitée et discordante en ce qui concerne la grossesse au cours la SpA et en particulier la période du post-partum. Par exemple, une revue de la littérature réalisée en 2021 a trouvé cinq études décrivant un rebond d'activité pendant la grossesse, deux une amélioration et deux une stabilité. Dans huit études, un rebond pendant la période du post-partum a été observé, deux études ont montré une stabilité (7). Néanmoins, la plupart de ces études sont basées sur des échantillons de petite taille et ont été publiées il y a plusieurs années, hormis deux études publiées récemment en 2016 et 2018.

Les données sont également contradictoires en ce qui concerne les complications au cours du péri et du post-partum dans la PR et la SpA, certaines études décrivant une survenue de complications similaire à la population générale

(8,9) et d'autres davantage de césariennes, de prématurités ou de prééclampsies (7,10–13).

En ce qui concerne les traitements, l'arsenal thérapeutique pour les rhumatismes inflammatoires chroniques (RIC) s'est amélioré ces dernières années, avec notamment le développement des biothérapies et thérapies ciblées (14,15).

Cependant, il n'y a pas de consensus sur la conduite thérapeutique appropriée pendant la grossesse ou le post-partum. Récemment, la British health professionals in rheumatology (BHRP) et la British society rheumatology (BSR) (16), l'European Alliance of Associations for Rheumatology (EULAR) (17) et plus récemment encore l'American college of rheumatology (ACR) (18) ont établi des recommandations concernant l'utilisation des traitements de fond pendant la grossesse et l'allaitement pour les patientes atteintes de RIC. Il était proposé l'utilisation sans contre-indication pendant la grossesse et l'allaitement des anti-TNFα et de la Sulfasalazine. Une réserve était émise quant à l'utilisation au cours du troisième trimestre en raison d'un risque potentiel d'infection péri-partum, excepté pour le certolizumab (CTZ). Le méthotrexate (MTX), le léflunomide, le tocilizumab, l'abatacept, le tofacitinib, l'ustekinumab et le secukinumab sont contre-indiqués pendant la grossesse et l'allaitement, principalement en raison d'un manque de données. L'ACR autorise l'utilisation du Rituximab (RTX) pendant l'allaitement. Il est cependant contre-indiqué pendant la grossesse.

La corticothérapie est autorisée pendant la grossesse et l'allaitement (16–18). L'ACR recommande l’utilisation d’une dose inférieure à 20 mg par jour (18). Pour l'EULAR et la BSR, il n'y a pas de limite de dose (16,17). En cas de doses élevées, un délai de 4 heures doit être respecté avant l'allaitement. Les anti-inflammatoires non

stéroidiens (AINS) peuvent être utilisés jusqu'au troisième trimestre et pendant l'allaitement.

Concernant l'allaitement, depuis 2001, l'Organisation Mondiale de la Santé (OMS) recommande un allaitement exclusif pendant les six premiers mois de la vie et la poursuite de l'allaitement jusqu'à l'introduction d'aliments sûrs et appropriés jusqu'à l'âge de deux ans (19,20). En France, le Collège National des Gynécologues et Obstétriciens Français (CNGOF) recommande, selon un accord professionnel, un allaitement maternel exclusif et prolongé de 4 à 6 mois (20). Les avantages de l'allaitement maternel sont multiples : meilleur développement cognitif de l'enfant, diminution des infections gastro-intestinales et respiratoires, perte de poids plus importante pour la mère, diminution du risque de dépression du post-partum, diminution du risque de cancer du sein, diminution du risque de diabète (21).

Il existe peu d'études sur l'allaitement dans la PR et moins encore chez les patientes atteintes de SpA (22,23). Des études antérieures ont montré que le recours à l'allaitement chez les patientes atteintes de PR était inférieur à celui de la population générale (24). La principale raison était la reprise des DMARDs (25). Cependant, des études plus récentes ont montré que les taux d'allaitement étaient comparables à ceux de la population générale (26,27). L'effet de l'allaitement sur les rhumatismes inflammatoires a également été peu étudié et les études qui s'y sont intéressées ont révélé des résultats contradictoires. En effet, au début des années 2000, plusieurs études ont décrit une activité plus importante chez les patientes allaitantes (28,29). Des études plus récentes ont montré un effet inverse (30–32).

Au regard du manque de données sur le post-partum aux cours des rhumatismes inflammatoires chroniques et du caractère contradictoire des données disponibles dans la littérature, notamment en termes d'activité, de complications et d'allaitement, nous avons cherché à décrire cette période chez des patientes atteintes de PR et de SpA au sein d'une cohorte prospective récente. Notre objectif était également de décrire l'approche thérapeutique, en l'absence de recommandations clairement établies. Nous nous sommes également intéressés à la relation entre l'allaitement et l'activité du rhumatisme dans le post-partum.

Impact of Postpartum on patients with inflammatory rheumatic diseases: the P2Rheum study

II. Introduction

Rheumatoid arthritis (RA) and Spondyloarthritis (SpA) are among the most frequent inflammatory rheumatic diseases (IRD). Their prevalence for women is around 0.47% to 0.66% (1) and about 0.5% (2) respectively.

The first study concerning the effect of pregnancy on RA was published in 1930s (3). A remission of RA was classically described during pregnancy then a rebound of activity during the postpartum (PP) period (4). However, more recent studies based on larger cohorts found lower rates of remission than previously described (5,6).

The literature is even more limited and discordant concerning pregnancy in SpA and especially the postpartum period. For example, a review of the literature conducted in 2021 found five studies describing a rebound of activity during pregnancy, two an improvement and two a stability. In eight studies, there was a rebound during the postpartum period, two studies showed stability (7). Nevertheless, most of these studies were based on small sample sizes and published several years ago, except for two published in 2016 and 2018.

Data are also inconsistent concerning postpartum outcomes in RA and SpA with some studies describing similar rates of complications compared to the general population (8,9) and others more caesarean sections (CS), prematurity or pre-eclampsia (7,10–13).

Regarding treatment, the therapeutic arsenal for IRD has improved in recent years. However, there is no consensus on the appropriate treatment for these patients, either during pregnancy or postpartum. Recently, the BSR and BHPR (16), the EULAR (17) and more recently the ACR (18) have established guidelines on the use of treatments

during pregnancy and lactation for patients with IRD. They agreed on the use without contraindications of TNF inhibitors and sulfasalazine in pregnancy and lactation. Others Biological Disease-Modifying AntiRheumatic Drugs (bDMARDs), Conventional synthetic Disease-Modifying AntiRheumatic Drugs (csDMARDs) and Targeted synthetic Disease-Modifying AntiRheumatic Drugs (tsDMARDs) are not recommended, mainly due to a lack of data. Corticosteroid therapy is approved during pregnancy and breastfeeding (16-18).

There are few studies focusing on breastfeeding in RA and especially in patients with SpA (22,23). For RA patients, it has been described in previous studies that the rate of breastfeeding was lower than in the general population (24). The main reason for discontinuation was the resumption of DMARDs (25). In more recent studies, breastfeeding rates were found to be comparable to the general population in patients with IRD (26,27). The effect of breastfeeding on IRD has also been poorly investigated and the studies that have focused on it have found conflicting results. At the beginning of the 2000s, several studies described a greater activity in breastfeeding patients (28,29). More recent studies showed an opposite effect (30–32).

In regards to the lack of data on the postpartum period in IRD and the contradictory nature of the data available in the literature, particularly in terms of activity, outcomes and breastfeeding, we sought to describe this period in patients with RA and SpA in a recent prospective cohort. Our aim was also to describe the therapeutic approach, in the absence of clearly established recommendations. We also focused on the relationship between breastfeeding and rheumatic disease activity in the postpartum period.

III. Materials and method

a. Population

We conducted a descriptive, retrospective study from a French prospective observational multicenter GR2 cohort ('Groupe de recherche sur la Grossesse et les Maladies Rares') studying pregnant women with IRD including RA and SpA (NCT02450396). This study is part of the European network of pregnancy registers in Rheumatology (EuNep) (33). Patients were included since October 2014 in 63 centers in France. Recruitment is still ongoing. Inclusion criteria are any patient with IRD who was seeking pregnancy or was pregnant. Women are included by their rheumatologists and followed until 12 months post-partum. Among the 442 patients with RA or SpA from the GR2-RIC cohort, 218 were included. The other patients were excluded due to a lack of data about pregnancy or postpartum follow-up.

b. Data collection

Data were collected during several regular pre-conception visits, visits during pregnancy and visits around 6 and 12 months after delivery, from October 2014 to October 2022. The inclusion visit collected sociodemographic data, the age of the patients and their history, the duration of their rheumatism as well as the main characteristics of their rheumatism (axial, peripheral, seropositive, erosive). Previous treatments were also described. At each visit, disease activity was assessed with DAS28-CRP for RA and BASDAI and ASDAS for SpA and flares were defined according to physician judgment. Breastfeeding was analyzed at delivery, at 6 and 12 months.

c. Outcomes

The main objective of the study was to describe the main characteristics of the postpartum period in patients with RA and SpA in a recent cohort, namely rheumatic activity, breastfeeding, treatments and complications at delivery and in the immediate postpartum. As secondary objective, the rate of breastfeeding and its possible impact on the activity of IRD were studied.

d. Scores

Different scores were used to evaluate the activity of the disease. We used as a threshold a BASDAI < 2 for remission and BASDAI ≥ 4 for high activity (34) . The thresholds for ASDAS-CRP were <1.3 for remission, between 1.3 and 2.1 for low activity, > 2.1 for moderate to high activity (34). For DAS28-CRP, the cutoff for remission was 2.6, for low activity between 2.6 and 3.2, and for medium to high activity > 3.2 (35).

e. Statistical analysis

Statistical analysis were performed using R software (version 4.1 or higher) and conducted at the Unité Statistique, Évaluation Économique, Data-management (SEED) of the Lille University Hospital. All statistical tests were two-sided with a first-species risk of 5%. The description was stratified in patients with SpA and those with RA. Categorical variables were described by numbers and percentages. Quantitative variables were described by the mean and standard deviation in case of a Gaussian distribution, or by the median and interquartile range (i.e., 25th and 75th percentiles) in the opposite case. The normality of the distributions was tested by a Shapiro-Wilk test and verified graphically by histograms.

Subgroup bivariate comparisons by IRD were performed according to patients' breastfeeding status (ongoing, completed, and never breastfed) at 6 and 12 months by Kruskal-Wallis tests for continuous variables and Fisher exact tests for categorical variables. The change in activity indices between each measurement time during follow-up (preconception, pregnancy, 6 months, and 12 months) was investigated by paired Student's t-tests or Mann-Whitney paired rank tests for quantitative variables or by Mac-Nemar Chi-2 tests for paired data for qualitative variables.

f. Ethics

Because all women received standard treatment, written informed consent was not required by French law. This project adheres to the principles of the Declaration of Helsinki and was approved by the Local Ethics Committee (CPP Ile de France VI, Groupe Hospitalier Pitié-Salpêtrière, 29 August 2012).

IV. Results

a. Population characteristics

i. Spondyloarthritis

Among the 218 patients studied, 124 patients suffered from SpA. The main characteristics of our population are listed in **table 1**. Mean age at the beginning of pregnancy was 31.8 (+/- 5.0) years. Majority of our patients suffered from axial SpA (76.6%). At delivery, 95/116 (81.9%) patients had vaginal deliveries, 21/116 (18.1%) by CS. The average term was 38.9 (+/- 1.8) weeks and 7/123 (5.7%) of the child were preterm.

Regarding outcomes at delivery, 59/116 (50.8%) patients presented complications at delivery. 31/79 (22.8%) were gravidic complications (gestational

diabetes, hypertension, premature rupture of the membranes, prematurity...), 11/79 (13.9%) were placental insufficiency (Pre-eclampsia / Eclampsia, HELLP (hemolysis, elevated liver enzymes and low platelet count), Retroplacental hematoma, Fetal growth anomaly) and 12/79 (15.2%) were fetal complications.

ii. Rheumatoid arthritis

94 patients with RA were included (**Table 1**). The mean age at the beginning of pregnancy was 32.0 (+/- (5.0) years. Half had erosive involvement, 66/92 (71.7%) were seropositive for rheumatoid factor and 65/92 (70.7%) for ACPA. At delivery, 60/83 (70.6%) patients had vaginal deliveries, 23/83 (7.0%) by CS. Term averaged 38.5 (+/- 2.1) weeks with 17/92 (18.0%) of preterm children.

46/84 (54.8 %) patients presented complications at delivery. We observed 28/57 (49.1%) gravidic complications, 3/57 (5.3%) placental insufficiency and 10/57 (17.5%) of fetal complications.

TABLE 1 : Population characteristics and outcomes

CHARACTERISTICS	**SPONDYLOARTHRITIS N= 124**	**RHEUMATOID ARTHRITIS N = 94**
Mean age at pregnancy, y (sd)	31.82 (5.0)	32.83 (5.0)
Mean duration of rheumatism, y (sd)	10.31 (6.1)	12.3 (7.7)
Axial SpA (%)	95 (76.6)	
Peripheric SpA (%)	58 (46.8)	
Erosive RA (%)		41/89 (44.6)
RF positive (%)		66/92 (71.7)
ACPA positive (%)		65/92 (70.7)
Parity (%)		
- primiparous	46/59 (78.0)	32/40 (80.0)
- multiparous	13/59(22.0)	8/40 (20.0)
Vaginal delivery (%)	95/116 (81.9)	60/83 (70.6)
Cesarean section (%)	21/116 (18.1)	23/83 (27.0)
*Complication during pregnancy (%)**	59/116 (50.8)	46/84 (54.8)
Type of complication:	79	57
- Gravidic (%)	31(39.2)	28 (49.1)
- Placental Insufficiency (%)	11(13.9)	3 (5.3)
- Infection (%)	19 (24.0)	13 (22.8)
- hemorrhage (%)	4 (5.1)	3 (5.3)
- thrombotic (%)	2 (2.5)	0 (0.0)
- fetal (%)	12 (15.2)	10 (17.5)
Mean term at delivery, w (sd)	38.9 (1.8)	38.3 (2.1)
Preterm (%)	7/123 (5.7)	17/92 (18.0)

Legends: Data are expressed in mean and standard deviation (sd) or number and percentages. Gravidic complications are defined as gravidic complications (gestational diabetes, hypertension, premature rupture of the membranes, SpA: spondylarthritis; RF: rheumatoid factor; ACPA : Anti-citrullinated protein antibody, sd: standard deviation
**Number of patients who presented complication*

b. Activity

i. Spondyloarthritis

1. Activity at 6- and 12-months post-partum

48/118 (40.7%) patients, presented 1 or several flares in the first 6 months postpartum, 35/54 (64.8%) flares occurred during the first 3 months (**Table 2**). At 6 months, 30/84 (35.7%) patients were in remission, 22/84 (26.2%) had low activity,

32/84 (38.1%) had moderate to severe activity. Between 6 and 12 months after delivery, 16/109 (13.5%) patients reported relapses, mostly in 9 to 12 months. At 12 months, 32/79 (40.5%) were in remission, 20/79 (25.6%) had low activity, 27/79 (34.1%) had moderate to severe activity.

2. Difference between pregnancy and post-partum

There were no significant differences in terms of activity (flares, BASDAI and the ASDAS-CRP) at 6 months PP compared to during pregnancy (**Table 3**). However, CRP level was significantly higher during pregnancy compared to postpartum at 6 months (7 mg/l vs 3.2 mg/l p = 0.014). At one-year PP, similar results for the BASDAI and the ASDAS-CRP were found (**Table 4**). The CRP level (5 mg/l vs 2.9 mg/l p = 0.003) and the number of flares (40,3% vs 13,4% p < 0,001) were significantly higher during pregnancy

3. Difference between the pre-conceptional period and post-partum

For the 25 patients for whom we had data, no significant difference was found in terms of activity, CRP level and BASDAI between the preconception period and the postpartum at 6 and 12 months (**Table 5 and 6**).

TABLE 2 : Activity and flares at 6 and 12 months

	POSTPARTUM 6 MONTHS				POSTPARTUM 12 MONTHS			
	SPONDYLOARTHRITIS		RHEUMATOID ARTHRITIS		SPONDYLOARTHRITIS		RHEUMATOID ARTHRITIS	
CRP, mg/l (sd)	52	6.39 (7.9)	63	8 .28 (20.7)	66	5.47 (7.3)	58	4.68 (7.2)
ESR, mm (sd)	38	19.11 (23.5)	38	17.18 (19.2)	42	10.02 (9.5)	40	14.05 (13.5)
BASDAI (sd)	83	2.93 (2.4)		-	79	2.59 (2.2)		-
ASDAS-CRP (sd)	39	2.31 (1.2)		-	39	1.70 (1.0)		-
DAS28-CRP (sd)		-	61	2.48 (1.2)		-	59	2.23 (1.1)
Tender joint count (sd)		-	75	3.16 (5.3)		-	71	2.70 (5.1)
Swollen joint count (sd)		-	75	1.72 (3.3)		-	71	0.90 (2.0)
Activity (%)	84		69		79		64	
Remission		30 (35.7)		39 (56.5)		32 (40.5)		43 (67.2)
Low		22 (26.2)		13 (18.8)		20 (25.3)		11 (17.2)
Moderate / High		32 (38.1)		17 (24.6)		27 (34.2)		10 (15.6)
FLARE (%)	118		92		109		91	
- Yes		48 (40.7)		57 (62.0)		16 (13.5)		32 (35.2)
- No		70 (59.3)		35 (38.0)		103 (86.6)		59 (64.8)
FLARE at delivery (%)	54	3 (5.6)	56	10 (17.9)		-		-
FLARE 1 to 3 months (%)	54	35 (64.8)	56	31 (55.4)		-		-
FLARE 3 to 6 months (%)	54	16 (29.6)	56	15 (26.8)		-		-
FLARE 6 to 9 months (%)		-		-	19	8 (42.1)	22	9 (40.9)
FLARE 9 to 12 months (%)		-		-	19	11 (57.9)	22	13 (59.1)

Legends: Data are expressed in in mean and standard deviation (sd) or number and percentages. Disease activity was defined for SpA according to BASDAI or ASDAS-CRP: : BASDAI < 2 for remission and BASDAI ≥ 4 for high activity ; ASDAS-CRP <1.3 for remission, ASDAS-CRP> 1.3 and <2.1 for low activity, ASDAS-CRP> 2.1 for moderate to high activity ; DAS28-CRP<2.6, for low activity, DAS28-CRP >2.6 and <3.2, and DAS28-CRP>3.2 for medium to high activity, sd: standard deviation; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; DAS28-CRP: Disease Activity Score based on 28 tender and swollen joints and C reactive protein.

ii. Rheumatoid arthritis

1. Activity at 6- and 12-months post-partum

57/92 (62.0%) patients, had 1 or several flares in the first 6 months of delivery, 31/56 (55.4%) flares occurred during the first 3 months (**Table 2**). Concerning disease activity, 39/69 (56.5%) were in remission, 13/69 (18.8%) had low activity, 17/69 (24.6%) had moderate to severe activity at 6 months. Between 6 and 12 months, 32/91 (35.2%) patients reported relapses (**Table 2**). At 12 months, 43/64 (67.2%) patients were in remission, 11/64 (17.2%) had low activity, 10/64 (15.6%) had moderate to severe activity.

2. Difference between pregnancy and post-partum

We observed significantly more flares in the first 6 months PP compared to pregnancy (43.5% vs 62% p = 0.02) (**Table 3**). CRP level was higher during pregnancy compared at 12 months (4.3 vs. 2 p = 0.004) (**Table 4**). On the contrary, the DAS28-CRP score was slightly higher at 12 months postpartum than during pregnancy (1.9 vs 2.1 p = 0.004). The number of flares were not different during pregnancy and at one-year PP.

TABLE 3: Comparison of activity during pregnancy and postpartum at 6 months

	SPONDYLOARTHRITIS				RHEUMATOID ARTHRITIS			
	N	PREGNANCY	POST-PARTUM (M6)	p	N	PREGNANCY	POST-PARTUM (M6)	p
FLARE (%)	118	48 (40.7)	48 (40.7)	0.999	92	40 (43.5)	57 (62.0)	**0.020**
ACTIVITY (%)	71			0.436				0.349
REMISSION		23 (32.4)	27 (38.0)			44 (68.8)	37 (57.8)	
LOW		28 (39.4)	19 (26.8)			7 (10.9)	12 (18.8)	
MODERATE/HIGH		20 (28.2)	25 (35.2)			13 (20.3)	15 (23.4)	
CRP (mg/l)	43	7.0 [3.3 ; 13.1]	3.2 [1.4 ; 5.1]	**0.014**	54	4.8 [2.3 ; 10.2]	2.6 [1.0 ; 9.8]	0.371
ESR (mm)	20	21.5 [11.8 ; 48.4]	9.0 [4.8 ; 22.5]	0.067	28	29.0 [16.8 ; 48.8]	14.0 [6.0 ; 27.5]	**0.004**
ASDAS-CRP	29	2.3 [1.7 ; 2.8]	2.2 [1.1 ; 3.0]	0.865	-	-	-	-
BASDAI	70	2.5 [1.3 ; 4.0]	2.0 [1.0 ; 4.0]	0.562	-	-	-	-
DAS28-CRP	-	-	-	-	54	2.1 [1.6 ; 3.0]	2.4 [1.5 ; 3.1]	0.409

Data are expressed in median and interquartile or number and percentages. Disease activity was defined for SpA according to BASDAI or ASDAS-CRP : BASDAI < 2 for remission and BASDAI ≥ 4 for high activity ; ASDAS-CRP <1.3 for remission, ASDAS-CRP> 1.3 and <2.1 for low activity, ASDAS-CRP> 2.1 for moderate to high activity ; DAS28-CRP<2.6, for low activity, DAS28-CRP >2.6 and <3.2, and DAS28-CRP>3.2 for medium to high activity, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; DAS28-CRP: Disease Activity Score based on 28 tender and swollen joints and C reactive protein.

TABLE 4 : Comparison of activity during pregnancy and postpartum at 12 months

	SPONDYLOARTHRITIS				RHEUMATOID ARTHRITIS			
	N	PREGNANCY	Post-partum (M12)	p	N	PREGNANCY	Post-partum (M12)	p
FLARE (%)	119	48 (40.3)	16 (13.4)	**<0.001**	91	40 (44.0)	32 (35.2)	0.280
ACTIVITY (%)	69			0.834	60			0.659
REMISSION		25 (36.2)	28 (40.6)			44 (73.3)	41 (68.3)	
LOW		25 (36.2)	19 (27.5)			7 (11.7)	11 (18.3)	
MODERATE/HIGH		19 (27.5)	22 (31.9)			9 (15.0)	8 (13.3)	
CRP (mg/l)	53	5.0 [3.0 ; 8.8]	2.9 [1.0 ; 7.9]	**0.003**	51	4.3 [2.3 ; 10.0]	2.0 [1.0 ; 3.8]	**0.004**
ESR (mm)	23	21.0 [7.5 ; 33.5]	6.0 [4.0 ; 13.5]	**0.003**	30	32.3 [21.9 ; 51.1]	10.5 [2.5 ; 18.3]	**<0.001**
ASDAS-CRP	30	1.9 [1.4 ; 2.7]	1.5 [1.0 ; 2.3]	0.092	-	-	-	-
BASDAI	69	2.7 [1.3 ; 4.0]	2.0 [1.0 ; 4.0]	0.118	-	-	-	-
DAS28-CRP	-	-	-	-	53	1.9 [1.5 ; 2.8]	2.1 [1.4 ; 2.7]	**0.004**

Data are expressed in median and interquartile or number and percentages. Disease activity was defined for SpA according to BASDAI or ASDAS-CRP : BASDAI < 2 for remission and BASDAI ≥ 4 for high activity ; ASDAS-CRP <1.3 for remission, ASDAS-CRP> 1.3 and <2.1 for low activity, ASDAS-CRP> 2.1 for moderate to high activity ; DAS28-CRP<2.6, for low activity, DAS28-CRP >2.6 and <3.2, and DAS28-CRP>3.2 for medium to high activity BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; DAS28-CRP: Disease Activity Score based on 28 tender and swollen joints and C reactive protein.

3. Difference between the preconceptional period and the postpartum period

For the 18 patients for whom we had data, no significant difference was found in terms of activity (CRP level and DAS28-CRP) between the preconception period and 6-month PP (**Table 5**). On the other hand, for the 15 patients we were able to compare, there was a significant difference between DAS28-CRP at preconception and at one-year PP (2.6 vs. 1.8 p=0.007) (**Table 6**).

TABLE 5 : Comparison of activity during preconceptionnal and 6-month PP

	SPONDYLOARTHRITIS				RHEUMATOID ARTHRITIS			
	N	**PRECONCEPTIONNAL**	**POST-PARTUM (M6)**	**p**	**N**	**PRECONCEPTIONNAL**	**POST-PARTUM (M6)**	**p**
ACTIVITY (%)	25			0.284				0.392
REMISSION		5 (20)	10 (40)		18	11 (61.1)	10 (55.6)	
LOW		10 (40)	5 (20)			1 (5.6)	4 (22.2)	
MODERATE/HIGH		10 (40)	10 (40)			6 (33.3)	4 (22.2)	
CRP (mg/l)	13	2.0 [1.0 ; 12.1]	4.0 [1.6 ; 14.0]	0.839	16	2.8 [1.0 ; 4.9]	3.0 [1.0 ; 11.3]	0.518
ESR (mm)	8	7.5 [5.0 ; 31.0]	17.0 [6.8 ; 39.0]	0.999	12	6.5 [4.5 ; 15.5]	6.0 [3.8 ; 16.0]	0.385
ASDAS-CRP	7	2.9 [1.3 ; 3.3]	3.7 [2.1 ; 3.9]	NA	-	-	-	-
BASDAI	25	3.0 [2.0 ; 5.0]	2.0 [1.0 ; 4.0]	0.543	-	-	-	-
DAS28-CRP	-	-	-	-	16	2.6 [1.8 ; 4.2]	2.5 [1.4 ; 3.3]	**0.033**

Data are expressed in median and interquartile or number and percentages. Disease activity was defined for SpA according to BASDAI or ASDAS-CRP : BASDAI < 2 for remission and BASDAI ≥ 4 for high activity ; ASDAS-CRP <1.3 for remission, ASDAS-CRP> 1.3 and <2.1 for low activity, ASDAS-CRP> 2.1 for moderate to high activity ; DAS28-CRP<2.6, for low activity, DAS28-CRP >2.6 and <3.2, and DAS28-CRP>3.2 for medium to high activity BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; DAS28-CRP: Disease Activity Score based on 28 tender and swollen joints and C reactive protein.

TABLE 6: Comparison of activity during preconceptionnal and 1-year PP

	SPONDYLOARTHRITIS				RHEUMATOID ARTHRITIS			
	N	**PRECONCEPTIONNAL**	**POST-PARTUM (M12)**	**p**	**N**	**PRECONCEPTIONNAL**	**POST-PARTUM (M12)**	**p**
ACTIVITY (%)	23			0.134	16			NA
REMISSION		5 (21.7)	7 (30.4)			9 (56.3)	12 (75.0)	
LOW		11 (47.8)	4 (17.4)			2 (12.5)	2 (12.5)	
MODERATE/HIGH		7 (30.4)	12 (52.2)			5 (31.3)	2 (12.5)	
CRP (mg/l)	18	4.0 [1.6 ; 10.0]	2.5 [1.0 ; 9.0]	0.394	15	3.0 [2.0 ; 5.9]	2.3 [1.0 ; 5.1]	0.368
ESR (mm)	8	7.0 [5.8 ; 13.0]	6.0 [5.5 ; 10.0]	0.235	12	9.5 [6.5 ; 17.0]	10.0 [6.5 ; 16.5]	0.695
ASDAS-CRP	9	2.4 [1.0 ; 3.0]	1.5 [0.7 ; 3.0]	0.652	-	-	-	-
BASDAI	23	2.0 [2.0 ; 5.0]	4.0 [1.0 ; 5.0]	0.726	-	-	-	-
DAS28-CRP	-	-	-	-	15	2.6 [2.0 ; 4.4]	1.8 [1.4 ; 2.7]	**0.007**

Data are expressed in median and interquartile or number and percentages. Disease activity was defined for SpA according to BASDAI or ASDAS-CRP : BASDAI < 2 for remission and BASDAI ≥ 4 for high activity ; ASDAS-CRP <1.3 for remission, ASDAS-CRP> 1.3 and <2.1 for low activity, ASDAS-CRP> 2.1 for moderate to high activity ; DAS28-CRP<2.6, for low activity, DAS28-CRP >2.6 and <3.2, and DAS28-CRP>3.2 for medium to high activity, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; DAS28-CRP: Disease Activity Score based on 28 tender and swollen joints and C reactive protein.

c. Breastfeeding

i. At delivery

For SpA patients, 64/115 (55.7%) patients breastfed at delivery (51/115 (44.3%) completely and 11/115 (10.0%) mixed) (**Figure 1**). The main reasons were a refusal to breastfeed (27.0%), a contraindication (7.8%) or an unknown reason (7.8%).

For RA, 46/82 (56.1%) patients breastfed at delivery (34/82 (41.5%) completely and 12/82 (14.6%) mixed) (Figure 1). The main reasons were a refusal to breastfeed (22.0%) or an unknown reason (15.9%).

ii. During the postpartum period

At 6 months, 20/109 (18.3%) patients with SpA were still breastfeeding and 32/109 patients (29.4%) stopped (**figure 1**). The mean duration of breastfeeding was 14.3 (+/- 10.9) weeks. For RA patients, at 6-month PP, 13/82 patients (15.9%) were still breastfeeding and 29/82 patients (35.4%) stopped. The mean duration of breastfeeding was 12.9 (+/- 10.0) weeks. Disease activity (BASDAI score, ASDAS, DAS28-CRP and number of flares) were similar between patients who breastfeed at six-month PP and patients who stopped or did not since the delivery for both populations.

At 12-month PP, 6/95 patients (6.3%) with SpA and 4/80 patients (5.0%) with RA were still breastfeeding. We could not perform statistical analysis tests because of a lack of data. Based on our data, there does not appear to be a difference between the three groups.

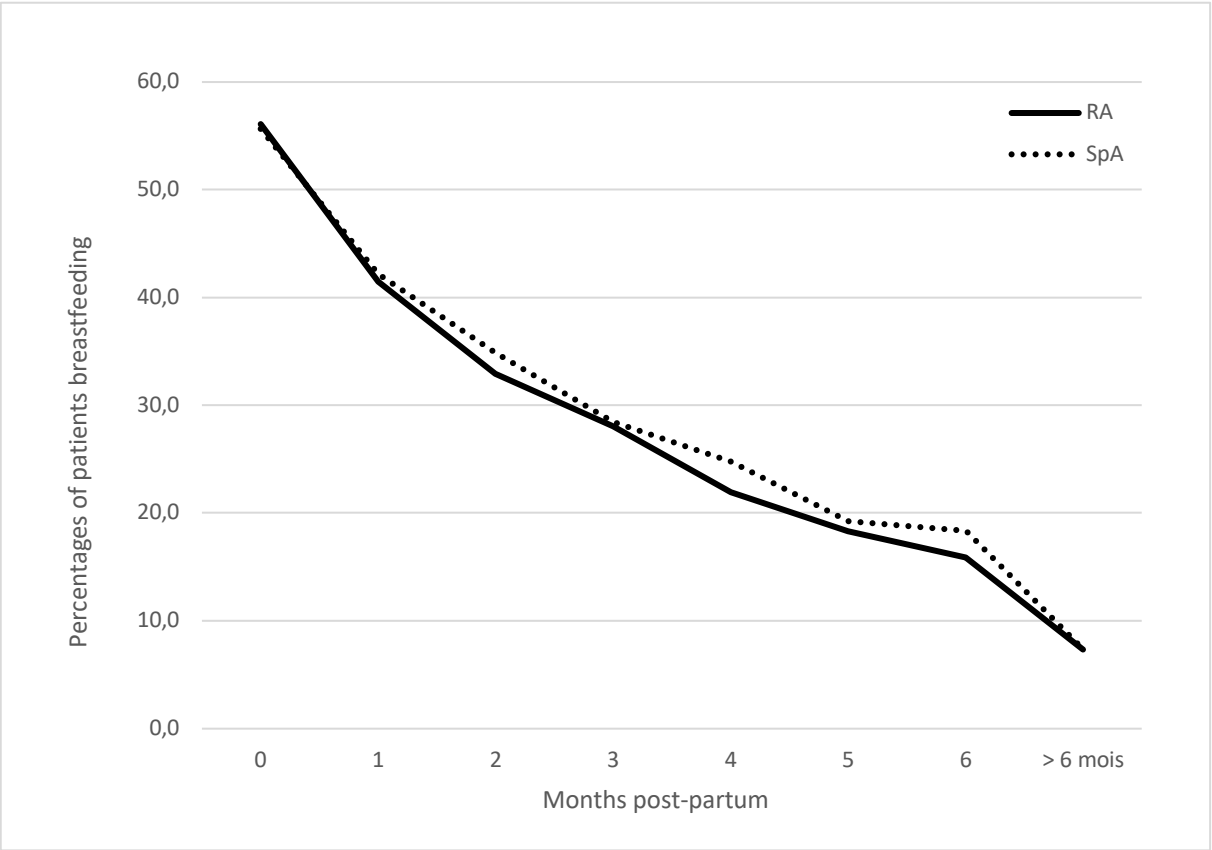

Figure 1 Percentages of patients Breastfeeding during post-partum.

Data are expressed in percentages. RA: Rheumatoid arthritis, SpA : spondylarthritis, 0 : at delivery

iii. Breastfeeding and treatments

19/64 (29.7%) patients with SpA and 16/46 (34.8%) patients with RA received bDMARD while breastfeeding. Among RA patients, 10 patients discontinued breastfeeding at the same period as resuming treatment. For SpA patients, there did not appear to be any relationship between resumption of treatment and discontinuation of breastfeeding.

d. Treatments

i. Spondyloarthritis

25/85 (29.4%) of patients treated with bDMARD during pregnancy discontinued treatment in the first trimester and 24/85 (28.2%) in the third trimester. bDMARDs were resumed during the PP period in 54/123 (43.9%) patients and initiated in 2/124 (1.6%) patients, in 42% of cases during the first month **(table 7).** All biotherapies were TNF inhibitors except for one treatment with belimumab (patients with SpA and systemic lupus erythematous). In total, 33/56 patients had CTZ, 20/56 etanercept (ETN), 18/56 adalimumab (ADA) and others infliximab (INF) or golimumab (GOL). MTX was started on average during the third month.

ii. Rheumatoid arthritis

Concerning bDMARDs, 15/48 (31.25%) of patients treated with bDMARD during pregnancy discontinued treatment in the first trimester and 17/48 (35.4%) in the third trimester. At delivery, only 15/92 (16.3%) patients received a DMARD **(Table 7)**. During the postpartum period, 39/91 patients (42.9%) resumed bDMARD and 6/91(6.6%) initiated a treatment, in 19/45 (42.2%) of cases during the first month, in 10/45 (22.2%) during the second**.** 38/45 (84.4%) bDMARDs were TNF-inhibitors, mainly ETN (20/47) and CZP (24/47). The remaining were tocilizumab, abatacept and JAK inhibitors.

7 patients had sulfasalazine during pregnancy and the postpartum period. 36/90 (40.0%) of patients started immunosuppressive treatments in the postpartum period, on average about 4 months after delivery. At delivery, 12/94 patients (12.8%) received corticosteroid therapy with a stable average dose of 8.2 mg/d (+/- 3.8), only 2 had a bDMARD associated. After delivery, 12 courses of corticosteroids were initiated with a mean maximum dose of 12.0 mg/d (+/- 11.0).

TABLE 7: Treatments use at delivery and in post-partum

	DELIVERY	RESUMED PP	INITIATED PP
SPA			
bDMARDS (%)	29/124 (23.4)	54/123 (43.9)	2/124 (1.6)
MTX (%)	0/124	6/123 (4.9)	3/123 (2.4)
CORTICOTHERAPIE (%)	5/124 (4.0)		3/123 (2.4)
RA			
bDMARDS (%)	15/92 (16.3)	39/91 (42.9)	6/91 (6.6)
MTX (%)	0/91	30/91 (33.0)	4/91 (4.4)
CORTICOTHERAPIE (%)	12/94 (12.8)		12/94 (12.8)

Legends: Date are expressed in number and percentages. SpA: Spondyloarthritis ; RA : rheumatoid arthritis; PP : post-partum; DMARDs : Disease-Modifying Antirheumatic Drugs ; MTX : Methotrexate.

V. Discussion

In our study, we found an increase in flares in the postpartum period compared to pregnancy in patients with RA with 62% of patients who presented flares, especially during the first three-month PP. It was generally accepted that RA improved during pregnancy and relapsed during the postpartum period (4). However, most of these studies were retrospective and not based on any biological markers or validated scores as DAS28 CRP. In 2008, one of the first prospective Dutch study using DAS28 CRP found patients with improvement in disease activity during pregnancy, particularly in the third trimester (5). There was a rebound of activity in the postpartum period for 39% of patients. A meta-analysis performed in 2018 on prospective studies also showed an improvement of disease activity during pregnancy for an average of 60% of patients, lower than previously described in literature (about 90%) (6). 47% of patients presented an increase in disease activity in the postpartum period.

We did not find any significant difference in diseases activity during pregnancy and at 6-month PP in patients with SpA, except for the CRP level, which was higher during pregnancy than postpartum at 6 and 12 months. It is known that the ESR increases during pregnancy but there is also a slight increase in CRP during pregnancy, which may partly explain our results for these parameters (36). We have noticed a higher number of relapses during pregnancy compared to one year after delivery for SpA patients. SpA activity during and after pregnancy is poorly described in the literature and results are contradictory (37). Recently, in a 2018 Norwegian study of 166 patients with axial SpA, a significant increase in BASDAI in the second trimester compared to the postpartum period was described (mean BASDAI 3.97 vs 3.46, p = 0.005) (38). The disease activity of SpA remained stable before pregnancy to 1-year PP and lower disease activity was found in the PP period. However, other studies have shown the opposite result (7).

In our study, we can observe that despite the stability of the disease in the postpartum period, 43.9% of our patients with SpA resumed bDMARD in the early post-partum. This could be an indirect marker of activity during the postpartum period, especially as 28% of patients treated during pregnancy stopped their bDMARD in the third trimester. This result was similar in the 2018 Norwegian study (38) with only 38% of patients who were on bDMARD 6 months after delivery, 11% on csDMARD, 7% on corticosteroids, and 44% on NSAIDs, despite a low disease activity.

For RA patients, only 42.9% resumed bDMARD during the PP period, mainly in the first month. A Dutch study based on the PreCARA cohort published in 2022, found results comparable to ours for RA: 46% of patients were on TNF inhibitors 6-month PP, 25% on MTX, 40% on corticosteroids (27). There was a clear increase in these

rates compared with the older PARA cohort (5,24). However, only 16% of our patients with RA received biotherapy at delivery and about 60% of patients treated at the beginning of pregnancy stopped their bDMARD in the first or third trimester. There may be a link between discontinuation of treatment during pregnancy, particularly in the last trimester, and resumption of activity in the postpartum period. Several studies have observed a significant association between discontinuing bDMARD before or during pregnancy and higher activity in the PP period (39–42). Rheumatic activity itself was also associated with a greater risk of relapse in the post-partum period. It is essential to maintain the lowest degree of disease activity before and during pregnancy, if necessary, with the use of bDMARD throughout the pregnancy.

Concerning breastfeeding and its impact, the rate at delivery was about 55% in patients with SpA and 56% in patients with RA, which is lower than the general population in France (about 70%) (21). In our study, about 1/3 continued breastfeeding at 6-month PP. The average duration of breastfeeding observed in our two populations was slightly lower than general population (about 14 weeks for SpA and 12 weeks for RA vs 15 weeks in general population (19)).

A Dutch study conducted from 2002 to 2008 in patients with RA and included in the PARA registry found a lower rate of breastfeeding than the general population: At 4-6, 12, and 26 weeks PP, 43%, 26%, and 9% were breastfeeding (24). This work was continued in 2022 with the PreCARA study and showed a breastfeeding rate comparable to the general population with 70% at delivery, 60% at 4-6 weeks, 39.8% at 12 weeks and 26% at 26 weeks (27). Another study was conducted in 2021 in the United States on 295 patients with rheumatics diseases, including 100 patients with RA or SpA (26). At delivery, 84% of the patients tried to breastfeed. At the PP visit, i.e.,

about 7.6 weeks, 2/3 of the patients continued to breastfeed (70%). A majority of patients discontinued breastfeeding because of a resumption of treatment, particularly a bDMARD. In our study, around 30% of our two populations received a bDMARD while breastfeeding. In the PreCARA study, one of the reasons for the higher breastfeeding rate compared with the historical cohorts was better knowledge of the treatments used during the postpartum period, particularly TNF inhibitors (27).

We did not find any significant differences of in term of activity between patients who were breastfeeding or who had breastfed and those who never had breastfed throughout the postpartum period. The effect of breastfeeding on the activity of IRD is discussed in the literature. A rebound in activity has been reported in some studies in RA patients who are breastfeeding, especially after a first pregnancy (29). One of the hypothesis was that breastfeeding maintains a higher level of prolactin during the PP period which could contribute to the higher activity of the disease in these patients (32). This information is discussed in the literature and other studies have not shown this relationship or even found a protective effect of breastfeeding (30,31,43). Furthermore, the role of prolactin as a pro- or anti-inflammatory effect remains debated (44). However, these studies are based on small numbers of patients. One reason why rheumatic activity may be higher in breastfeeding patients is that they did not resume treatment during breastfeeding. With the improved knowledge of treatment during breastfeeding, this effect could no longer be seen. (27).

Finally, concerning outcomes at delivery and in the early postpartum, we described a CS rate of 18% for patients with SpA. Our result is comparable to the general population in France with a rate of about 15 to 20% of CS (45). This is lower

than those described in previous studies. The recent Swedish study published 2023 found a rate of elective CS in SpA higher than in the control group, but there was no difference in emergency CS (46). It was also described a decrease in the use of CS during the study of approximately 0.5% per year. In our study, we did not separate elective and emergency CS, which may explain the lower results than in previous studies. Another complication described in previous studies was prematurity. In our study, we observed a rate of 5,7% of preterm child. In the Swedish study of 2023, there was a significant difference compared to the control group (6.3% vs 4.3% OR 1.43 (1.13-1.80)) (46). This rate also tended to decrease over time with a rate of 5.1% between 2017 and 2020, thus comparable to ours. Regarding vascular complications such as pre-eclampsia or HELLP, our results are similar to those described in the literature with a higher rate than in the general population (11,46).

Concerning RA, we described a CS rate of 27% and 18% of preterm child. This is comparable to previous reports in the literature. For example, a 2022 U.S. Study examining the effects of pregnancy on RA patients found a significant higher rate of CS compare to control group (44% vs. 33% p= 0.02), a higher proportion of premature births (27% vs 13% p < 0,001) (9). Rate of pre-eclampsia were similar in both groups but more important than general population (3-4%) and in our population.

The strengths of our study are the multicenter design, the number of patients especially for patients with SpA which is higher than many early studies in the literature, and the prospective recruitment. Very few studies have focused on this postpartum period, particularly on the therapeutic attitude or the effect of breastfeeding, making our work original.

The main limitation is the lack of data, especially on biological markers such as CRP and on activity scores. We did not have the same number of visits during pregnancy for each patient and few preconception visits. We compensated by using an average of the activity during the pregnancies in order to compare them with those of the post-partum. There are also a number of patients that we were unable to include in this study, either because they had not yet given birth at the time of the study or because we did not have postpartum follow-up and therefore data on their disease activity.

In conclusion, RA patients presented significantly more flares in the first 6 months of postpartum compared to pregnancy while SpA patients remained stable. Yet, in both diseases, only about 40% of the patients resumed bDMARD during post-partum period. Breastfeeding was not associated with an increase or decrease in disease activity in SpA and RA patients. A better knowledge of this high-risk period as well as of the effects of the treatments would allow a better control of these patients throughout their pregnancy and in a prolonged way during the post-partum period.

VI. Discussion Générale

Dans notre étude, nous avons constaté une augmentation du nombre de poussées en post-partum par rapport à la grossesse chez les patientes atteintes de PR, 62 % d'entre elles ayant présenté des poussées, en particulier au cours des trois premiers mois du post-partum. Il était généralement admis que l'activité de la PR s'améliorait pendant la grossesse et rechutait pendant la période post-partum (4). Cependant, la plupart de ces études étaient rétrospectives et ne reposaient pas sur des marqueurs biologiques ou des scores validés tels que le DAS28-CRP. En 2008, l'une des premières études prospectives hollandaises utilisant le DAS28-CRP a observé une amélioration de l'activité de la maladie au cours de la grossesse, en particulier au cours du troisième trimestre (5). Un rebond d'activité a été observé dans le post-partum pour 39 % des patientes. Une méta-analyse réalisée en 2018 sur des études prospectives a également montré une amélioration de l'activité de la maladie pendant la grossesse pour environ 60% des patientes, inférieure à celle décrite précédemment dans la littérature (environ 90%) (6). 47% des patientes ont récidivé en post-partum.

Nous n'avons pas remarqué de différence significative en termes d'activité pendant la grossesse et 6 mois après l'accouchement chez les patientes atteintes de SpA, à l'exception du dosage de la CRP qui était plus élevé pendant la grossesse que dans le post-partum à 6 et 12 mois. Il est connu que la vitesse de sédimentation augmente pendant la grossesse mais on retrouve également une légère augmentation de la CRP, ce qui peut expliquer en partie nos résultats (36).

D'autre part, nous avons retrouvé un nombre plus élevé de rechutes pendant la grossesse qu'un an après l'accouchement. L'activité de la SpA pendant et après la grossesse est peu décrite dans la littérature et les résultats sont contradictoires (37). Dans une étude norvégienne de 2018 portant sur 166 patients atteints de SpA axiale, une augmentation significative du BASDAI au cours du deuxième trimestre par rapport au post-partum a été décrite (BASDAI moyen 3,97 contre 3,46, p = 0,005) (38). L'activité de la SpA est restée stable avant la grossesse jusqu'à un an après l'accouchement et une activité plus faible de la maladie a été constatée dans le post-partum. Cependant, d'autres études ont montré le résultat inverse (7). Dans notre étude, nous pouvons observer que malgré la stabilité de la maladie dans la période post-partum, 43,9% de nos patientes atteintes de SpA ont repris des bDMARDs dans le post-partum précoce. Cela pourrait être un marqueur indirect de l'activité de la maladie pendant la période post-partum, d'autant plus que 28% de celles qui étaient sous bDMARD au cours de la grossesse l'ont arrêté au troisième trimestre. Ce résultat était similaire dans l'étude de 2018 (38) avec 38% des patientes qui étaient sous bDMARD 6 mois après l'accouchement, 11% sous csDMARD, 7% sous corticostéroïdes et 44% sous AINS.

Concernant les patientes atteintes de PR, seulement 42,9 % des patientes ont repris un traitement par bDMARD pendant le post-partum, principalement au cours du premier mois. Une étude hollandaise basée sur la cohorte PreCARA publiée en 2022, a trouvé des résultats comparables aux nôtres pour la PR : 46% des patientes étaient sous anti-TNFα 6 mois après l'accouchement, 25% sous MTX, 40% sous corticostéroïdes (27). Ces taux ont nettement augmenté par rapport à la cohorte PARA plus ancienne (5,24). Cependant, seulement 16 % de nos patientes atteintes de PR

recevaient un bDMARD à l'accouchement et environ 60% des patientes traitées au cours de la grossesse arrêtent leur traitement au premier ou au troisième trimestre. Il peut exister donc un lien entre l'arrêt du traitement pendant la grossesse, en particulier au cours du dernier trimestre et la reprise de l'activité dans la période post-partum. Plusieurs études ont observé une association significative entre l'arrêt des bDMARD avant ou pendant la grossesse et une activité plus importante dans la période post-partum (39-42). L'activité rhumatismale elle-même était également associée à un risque accru de rechute dans la période post-partum. Il est essentiel de maintenir le plus bas niveau d'activité de la maladie avant et pendant la grossesse, si nécessaire, avec l'utilisation d'un bDMARD pendant toute la durée de la grossesse.

Concernant l'allaitement et son impact, le taux à l'accouchement était d'environ 55% chez les patients atteints de SpA et de 56% chez les patients atteints de PR, ce qui est inférieur à la population générale en France (environ 70%) (21). Dans notre étude, 1/3 poursuivaient l'allaitement à 6 mois. La durée moyenne d'allaitement observée dans nos deux populations est légèrement inférieure à celle de la population générale (environ 14 semaines pour les SpA et 12 semaines pour les PR vs 15 semaines dans la population générale (19)).

Une étude hollandaise menée de 2002 à 2008 auprès de patientes atteintes de PR et incluse dans le registre PARA a révélé un taux d'allaitement inférieur à celui de la population générale : À 4-6, 12 et 26 semaines après l'accouchement, 43 %, 26 % et 9 % des patientes allaitaient (24). Ces travaux ont été poursuivis en 2022 avec l'étude PreCARA et ont montré un taux d'allaitement finalement comparable à la population générale avec 70 % à l'accouchement, 60 % à 4-6 semaines, 39,8 % à 12 semaines et 26 % à 26 semaines (27). Une autre étude a été menée en 2021 aux

Etats-Unis sur 295 patientes atteintes de maladie inflammatoire, dont 100 patientes atteintes de PR ou de SpA (28). Lors de l'accouchement, 84% des patientes essayaient d'allaiter. A la visite postnatale, soit environ 7,6 semaines, 2/3 des patientes continuaient d'allaiter (70%). Une majorité de patientes ont arrêté l'allaitement en raison de la reprise d'un traitement de fond, en particulier un DMARD. Dans notre étude, environ 30% de nos deux populations ont bénéficié d'un bDMARD pendant leur allaitement. Dans l'étude PreCARA, une des raisons du taux d'allaitement plus élevé par rapport aux cohortes historiques était une meilleure connaissance des traitements utilisés pendant le post-partum, en particulier anti-TNFa (27).

Nous n'avons pas trouvé de différences significatives en termes d'activité entre les patientes qui allaitaient ou qui avaient allaité et celles qui n'avaient jamais allaité pendant toute la période du post-partum. L'effet de l'allaitement sur l'activité des rhumatismes inflammatoires est discuté dans la littérature. Certaines études font état d'un rebond de l'activité chez les patientes atteintes de PR qui allaitent, en particulier après une première grossesse (29). L'une des hypothèses est que l'allaitement maintient un niveau plus élevé de prolactine pendant la période post-partum, ce qui pourrait contribuer à l'activité plus élevée de la maladie chez ces patientes (32). Cette information est discutée et d'autres études n'ont pas montré cette relation ou ont même constaté un effet protecteur de l'allaitement (30,31,44). De plus, le rôle de la prolactine en tant qu'effet pro- ou anti-inflammatoire reste débattu (44). Cependant, ces études sont anciennes et basées sur un petit nombre de patients. L'une des raisons pour lesquelles l'activité rhumatismale peut être plus élevée chez les patientes qui allaitent est qu'elles n'ont pas repris leur traitement pendant l'allaitement. Avec l'amélioration

des connaissances sur le traitement pendant l'allaitement, cet effet pourrait ne plus être observé. (27).

Enfin, concernant les complications à l'accouchement et au cours du post-partum immédiat, nous avons décrit un taux de césariennes de 18% pour les patientes atteintes de SpA. Notre résultat est comparable à la population générale en France avec un taux d'environ 15 à 20% (45). Ce taux est inférieur à ceux décrits dans les études précédentes. La récente étude suédoise publiée en 2023 retrouvait un taux de césarienne programmée chez les SpA plus élevé que dans le groupe contrôle, en revanche il n'y avait pas de différence pour les césariennes réalisées en urgence (46). Il a également été décrit une diminution du recours à la césarienne d'environ 0,5% par an. Dans notre étude, nous n'avons pas séparé les césariennes programmées et celles réalisées en urgence, ce qui peut expliquer les résultats plus faibles. La prématurité est une autre complication décrite dans les études précédentes. Dans notre étude, nous avons observé un taux de 5,7% d'enfants prématurés. Dans l'étude suédoise de 2023, on retrouvait une différence significative par rapport au groupe témoin (6,3% vs 4,3% OR 1,43 (1,13-1,80)) (46). Ce taux avait également tendance à diminuer dans le temps avec un taux de 5,1% entre 2017 et 2020, donc comparable au nôtre. Concernant les complications vasculaires telles que la prééclampsie ou le HELLP syndrome, nos résultats sont similaires à ceux décrits dans la littérature avec un taux plus élevé que dans la population générale (11,46).

En ce qui concerne la PR, nous avons décrit un taux de césariennes de 27% et 18% d'enfants prématurés. Ces chiffres sont comparables aux rapports précédents de la littérature. Par exemple, une étude américaine de 2022 portant sur les effets de la

grossesse chez les patientes atteintes de PR a révélé un taux significativement plus élevé de césarienne par rapport au groupe témoin (44 % contre 33 % p = 0,02), ainsi qu'une proportion plus élevée de naissances prématurées (27 % contre 13 % p < 0,001) (9). Le taux de prééclampsie était similaire dans les deux groupes mais plus important que dans la population générale (3-4%) et que dans notre population.

Les points forts de notre étude sont la conception multicentrique, le nombre de patientes en particulier pour les patientes atteintes de SpA qui est plus élevé que de nombreuses études antérieures dans la littérature, et le recrutement prospectif. Très peu d'études se sont intéressées à cette période du post-partum, en particulier à l'attitude thérapeutique ou à l'effet de l'allaitement, ce qui fait l'originalité de notre travail.

La principale limite est le manque de données, notamment concernant les marqueurs biologiques comme la CRP ou sur les scores d'activité. Nous n'avons pas eu le même nombre de visites pendant la grossesse pour chaque patiente et peu de visites préconceptionnelles. Nous avons compensé en utilisant une moyenne de l'activité pendant les grossesses afin de les comparer avec celles du post-partum. Il existe également un certain nombre de patientes que nous n'avons pas pu étudier dans la cohorte, celles-ci n'ayant pas encore accouché au moment de l'étude, ou par manque de suivi post-partum et donc de données concernant l’activité de leur maladie.

En conclusion, les patientes atteintes de PR ont présenté un nombre significativement plus élevé de poussées au cours des six premiers mois du post-partum par rapport à la grossesse, tandis que les patientes atteintes de spondylarthrite ankylosante sont restées stables. Cependant, dans les deux populations, seulement

40 % des patientes ont repris un traitement bDMARD pendant la période post-partum. L'allaitement n'a pas été associé à une augmentation ou à une diminution de l'activité de la maladie chez les patientes atteintes de SpA et de PR. Une meilleure connaissance de cette période à risque ainsi que des effets des traitements permettrait une meilleure prise en charge de ces patientes tout au long de leur grossesse et de façon prolongée pendant le post-partum.

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Date de soutenance : 19 juin 2023
Titre de la thèse : L'effet du post partum sur les patientes atteintes de rhumatismes inflammatoires chroniques

Thèse - Médecine - Lille « 2023 »
Cadre de classement : Rhumatologie
DES + FST/option : Rhumatologie
Mots-clés : post-partum, polyarthrite rhumatoïde, spondylarthrite, grossesse, allaitement, rhumatisme inflammatoire chronique.

Contexte : Il existe peu de données sur l'impact de la période du post-partum (PP) sur l'activité des rhumatismes inflammatoires chroniques (RIC) et les données disponibles sur l'impact de l'allaitement sur l'activité des RIC sont contradictoires. Les objectifs de cette étude étaient de décrire l'activité de la maladie, les complications à l'accouchement et les traitements reçus pendant la période du PP, ainsi que la fréquence de l'allaitement et son impact possible sur l'activité des RIC.
Méthode : Nous avons mené une étude descriptive à partir de la cohorte observationnelle prospective multicentrique française (GR2) étudiant les femmes enceintes souffrant de RIC. Les données ont été recueillies au cours de plusieurs visites pré conceptionnelles régulières, de visites au cours de la grossesse et de visites autour de 6 et 12 mois PP, d'octobre 2014 à octobre 2022. L'activité de la maladie a été évaluée à l'aide du DAS28-CRP pour la PR et du BASDAI et de l'ASDAS pour la SpA. Les poussées ont été définies selon le jugement du médecin.
Résultats : 124 patientes atteintes de SpA et 94 patientes atteintes de PR ont été incluses. Chez les patientes atteintes de SpA, il n'y avait pas de différences significatives en termes d'activité à 6 mois PP par rapport à la grossesse contrairement aux patientes atteintes de PR ont présenté significativement plus de poussées au cours des 6 premiers mois PP qu'au cours de la grossesse (43,5 % vs 62 % p = 0,02). Il n'y avait pas de différence en termes d'activité de la maladie entre les patientes qui allaitaient, celles ayant allaité et celles n'ayant jamais allaité, à 6 et 12 mois PP. 29/124 patientes atteintes de SpA (23.9%) et 15/92 patientes atteintes de PR (16.3%) avaient des bDMARDs au moment de l'accouchement. Un bDMARDs a été repris au cours du post-partum chez 54/124 (45.3%) patientes atteintes de SpA et 39/91 patientes (42.9%) atteintes de PR. La plupart du temps un anti-TNFa.
Conclusion : Les patientes atteintes de PR ont présenté un nombre significativement plus élevé de poussées au cours des six premiers mois du PP par rapport à la grossesse, tandis que les patientes atteintes de SpA sont restées stables. Dans les deux populations, seulement 40 % des patientes ont repris un traitement bDMARD pendant le PP. L'allaitement n'a pas été associé à une augmentation ou à une diminution de l'activité de la maladie chez les patientes atteintes de SpA et de PR.

Composition du Jury :

Président : Le Professeur René-Marc FLIPO
Assesseurs : Le Professeur Damien SUBTIL, le Docteur Anna MOLTO,
Directeur de thèse : le Docteur Jean-Guillaume LETAROUILLY