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Pregnancy in juvenile idiopathic arthritis: maternal and foetal outcome, and impact on disease activity

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Abstract

Objective: This retrospective cohort study describes the modulation of disease activity during gestation and in the year following delivery as well as maternal and neonatal outcomes in a monocentric cohort of women with juvenile idiopathic arthritis (JIA).

Methods: Disease activity was assessed using DAS28-CRP before conception and every 3 months during pregnancy and in the first year postpartum. The risk of complicated pregnancies was measured applying a generalized estimating equation model. Changes in disease activity during gestation and in the first year postpartum were assessed in a linear mixed model for repeated measures.

Results: Thirty-one women (49 pregnancies) with persisting JIA and at least one conception were enrolled. Adjusted DAS28-CRP levels remained stable from preconception through the first trimester, but increased significantly in the second and decreased not significantly in the third. In the postpartum, adjusted disease activity peaked at 3 months after delivery, stabilized at 6 months to decrease at 1 year, although not significantly. Preconceptional DAS28-CRP and number of biological drugs predicted disease activity fluctuation during gestation. The number of biological drugs and the length of gestational exposure to biologics significantly predicted pregnancy morbidity. In particular, JIA women had a higher probability of preterm delivery compared with healthy and disease controls. Adjusted for breastfeeding and DAS28-CRP score in the third trimester, postconceptional exposure to biologics was inversely related with disease activity in the postpartum: the longer the patient continued treatment, the lower the probability of experiencing an adverse pregnancy outcome.

Conclusion: These data offer novel insights on how treatment affects disease activity during pregnancy and postpartum as well as obstetric outcomes in women with JIA.

Keywords: disease activity, juvenile idiopathic arthritis, obstetric outcome, postpartum, pregnancy, treatment

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Introduction

In the past, women with rheumatic conditions were reluctant to become pregnant because of several clinical, physical, and psychosocial barriers. Over the last decade, most of these barriers have collapsed due to the raising of awareness on reproduction issues in rheumatic diseases among both patients and clinicians and thanks to the outstanding improvement in disease control, which have rendered childbearing a feasible option for rheumatologic patients. Women with juvenile idiopathic arthritis (JIA) make no exception in the rheumatology scenario, and have experienced an increasing desire for motherhood. Not surprisingly, literature on this topic has recently flourished, but unfortunately available data

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regarding obstetric and neonatal outcomes in JIA are still scanty and not consistent. Evidence suggests that the main complications in JIA include a higher risk of preterm delivery and low birth weight, but no clinical predictor of adverse maternal and foetal outcome has yet been identified.[1–9] Discordant results concern the fluctuation of JIA disease activity during pregnancy. Earlier studies have suggested amelioration during gestation, and such clinical improvement was ascribed to the pregnancy-related immunomodulation that ultimately leads to a tolerogenic environment at the feto-maternal interface.[1,10,11] Recently, a high rate of flares during gestation has been reported, possibly attributable to the better preconceptional disease control due to the wider therapeutic armamentarium.[8,12–14] Young women with JIA may embark on pregnancy with long-standing disease duration: childhood-onset arthritis can start even on the first years of life and, despite the revolutionized therapeutic approach, in at least half of cases the disease persists into adulthood.[15] The enduring inflammatory burden at ages of bone accretion affects growth and can result in irreversible articular damage. Before obtaining disease remission, patients with JIA are usually prescribed with synthetic and biologic disease-modifying antirheumatic drugs (sDMARDs and bDMARDs), but the impact on reproduction of this long-lasting exposure needs to be further clarified. Most data have been raised in population-based studies analysing administrative health databases or hospital discharge records, which do not allow to adequately account for potential confounders, such as medications before and during pregnancy, JIA category, and disease activity.

We hereby describe the modulation of disease activity during gestation and in the year following delivery as well as maternal and neonatal outcomes in a monocentric cohort of women with JIA, carefully accounting for medications and disease features thanks to a detailed statistical analysis.

Materials and methods

Women aged more than 18 years and regularly attending our outpatient transition clinic from 2000 to 2020 were consecutively included in this retrospective cohort study in case of (1) JIA diagnosis formulated according to ILAR criteria, (2) persistence of disease activity into adulthood, and (3) at least one conception. Patients were further classified in disease categories according to ILAR criteria: oligoarticular, polyarticular, enthesitis-related arthritis, psoriatic, and systemic JIA.[16] All pregnant JIA women were followed-up monthly in a joint rheumatologic/obstetric clinic. Clinical data were retrospectively collected from medical records. Disease activity was assessed using DAS28-CRP before conception and then every 3 months during pregnancy and in the first year postpartum. Disease activity was defined upon DAS28-CRP scores as follows: remission (DAS28-CRP < 2.6), low ($2.6 \leqslant$ DAS28-CRP $<$ 3.2), moderate ($3.2 \geqslant$ DAS28-CRP $\leqslant 5.1$) and high disease activity (DAS28-CRP > 5.1).[17] Disease flares were defined as an increase in DAS28-CRP above 1.2.

Pregnancy morbidity (PrM) was defined as follows:

- Early pregnancy loss (PrL): unexplained spontaneous abortion before 10 gestational weeks (gw);
- Late PrL: unexplained spontaneous abortion at or beyond 10 gw;
- Premature delivery of a morphologically normal neonate before 37 gw.

When PrL could be explained by identifiable factors (e.g. extra-uterine pregnancy, chromosomal abnormalities, elective pregnancy termination), the pregnancy was excluded from the analysis. Babies with a birth weight below the 10th percentile for gw were defined as small for gestational age (SGA). All women attending the clinics were specifically questioned about delayed and abundant menses in order to rule out biochemical pregnancies.

Therapeutic options were discussed with each woman, and all patients consented to treatment.

The prevalence of maternal and foetal outcomes in JIA were compared with the prevalence of adverse outcomes in two control groups: 100 healthy controls (HCs, 173 pregnancies) attending a general obstetric clinic in the same institution and 228 patients with systemic autoimmune rheumatic diseases (SARDs, 392 pregnancies) with negative antiphospholipid antibodies (aPL) attending the joint rheumatologic/obstetric clinic.

The local ethics committee approved the study (Comitato Etico Milano Area B, Milan, Italy; authorization 629_2017bis – PROMAMMA study obtained on 24 October 2017); informed

consent was not obtained from participating subjects due to the retrospective design but all patient details have been de-identified.

The reporting of this study conforms to the STROBE statement for cohort studies.[18]

Statistical analysis

Descriptive statistics were generated for demographic and clinical data. As pregnancy outcomes are correlated within the same woman, a generalized estimating equation (GEE) model was applied. Changes in disease activity during gestation and the first year postpartum were assessed evaluating DAS28-CRP at different time-points in a linear mixed model with random intercept. A three-level model was applied: time-points were nested within pregnancies, and pregnancies were nested within women. The following variables were tested in the multivariate statistical models as coviarates and/or confounders: age at conception, age at disease onset, positivity for antinuclear antibodies (ANA), iridocyclitis, number of preconceptional sDMARDs, number of preconceptional bDMARDs, days of postconceptional bDMARD exposure, postpartum bDMARD exposure, prednisone >7.5 mg daily during pregnancy, preconceptional DAS28-CRP, DAS28-CRP in the three trimesters and in the postpartum and breastfeeding. Statistical model also assessed the interaction between time-points and time to introduction of bDMARD after delivery. Variables were retained in the models as confounders in case of contribution to the estimate of the main predictor ⩾10%. A p value <0.05 was considered statistically significant. Data were analysed using R version 3.4.0.

Results

Among the 31 women fulfilling the inclusion criteria, oligoarthritis was the most frequent JIA category (55%), followed by polyarthritis (29%). All women had long-standing disease duration, and three patients had required hip replacement (9.6%, bilateral in two cases; Table 1). Most patients had a refractory disease, as documented by the high number of both sDMARDs and bDMARDs required to control disease activity before conception. Two patients had arterial hypertension (5.4%); endometriosis and phenylketonuria were diagnosed in a single case each (2.7%). None of the patients consumed tobacco during gestation; three women (8.1%) had a BMI >30. None of the patients carried anti-Ro antibodies, while one woman had isolated positive anticardiolipin IgM at medium-high titers and an uncomplicated pregnancy without prophylactic treatment.[19]

During the study period, 49 pregnancies were observed. Forty-three pregnancies (87.8%) were exposed to bDMARDs, mostly to agents targeting tumour necrosis factor-alpha (TNF-α, etanercept (20 women), adalimumab (4) golimumab (8) and certolizumab (5)). Three pregnancies occurred in women exposed to rituximab in gT1, while exposure to sarilumab, abatacept and tocilizumab occurred in a single pregnancy each. In case of on-going bDMARDs, medications were discontinued at positive pregnancy test in 9 cases (20.9%), while 31 women continued bDMARDs during gT1 (72%), in agreement with available recommendations.[20] In three pregnancies (7.0%), treatment with certolizumab (two cases) and etanercept was continued throughout gestation. Two patients had a peri-conceptional exposure to methotrexate (MTX), one patient continued leflunomide for 1 month after conception. Three patients were on cyclosporine at the time of conception, and treatment was discontinued at a median of 40 days after conceiving. Therapy with azathioprine in a single patient was continued throughout pregnancy. Treatment with prednisone was on-going at the time of conception in 14 pregnancies, at a median daily dose of 5 mg.

Disease activity during pregnancy

In most cases, disease was satisfactorily controlled at conception: remission was obtained in 32 cases (65.3%) and low disease activity in 8 cases (16.3%). In six cases (12.2%%), women had a moderate disease activity; a single patient with psoriatic arthritis (2.0%) had high disease activity from preconception through the second gestational trimester (gT2). Data were missing in two pregnancies. In gT2, disease was moderately active in two additional pregnancies, both in patients with psoriatic arthritis.

Disease flare occurred in 10 pregnancies (23.3%), 5 (11.6%) in gT1, and 5 (13.5%) in T3. Gestational flares were more common in psoriatic arthritis, complicating three of seven pregnancies. Four out of the 10 flares we observed during gestation occurred in women with preconceptional exposure to biologics (two etanercept, one sarilumab, and one rituximab). The remaining flares

Table 1. Details of pregnancies subgrouped upon disease category.

All pregnancies	O-JIA ($n = 29$)	P-JIA ($n = 10$)	PsA + ERA ($n = 7$)	S-JIA ($n = 3$)	Total cohort ($n = 49$)
Age at first conception, mean (SD)	29.1 (4.7)	31.2 (4.0)	34.4 (6.1)	31.0 (2.0)	30.4 (4.9)
Age at JIA onset, median (IQR)	4.0 (7.0)	12.5 (2.0)	14.0 (10.0)	1.2 (2.4)	6.0 (9.3)
Disease duration in years, median (IQR)	23.0 (9.0)	19.0 (5.8)	23.0 (14.0)	29.0 (4.0)	22.0 (10.0)
ANA positivity, % (*n*)	72.4 (21)	30.0 (3)	42.9 (3)	0.0 (0)	55.1 (27)
Rheumatoid factor, % (*n*)	0.0 (0)	20.0 (2)	0.0 (0)	0.0 (0)	4.1 (2)
ACPA, % (*n*)	0.0 (0)	0.0 (0)	10.0 (1)	0.0 (0)	2.0 (1)
Iridocyclitis, % (*n*)	44.8 (13)	10.0 (1)	0.0 (0)	0.0 (0)	28.6 (14)
No. of preconceptional sDMARDs, median (IQR)	2.0 (1.0)	2.0 (0.8)	3.0 (2.0)	2.0 (0.5)	2.0 (1.0)
No. of preconceptional bDMARDs, median (IQR)	2.0 (1.0)	2.0 (0.8)	3.0 (1.0)	2.0 (0.5)	2.0 (1.0)
Comorbidities, % (*n*)	6.8 (2)	10.0 (1)	0.0 (0)	0.0 (0)	6.1 (3)

ACPA, antibodies against cyclic citrullinated peptides; ANA, antinuclear antibodies; bDMARDs, biological DMARDs; ERA, enthesitis-related arthritis; IQR, interquartile range; *n*, number; O-JIA, oligoarticular juvenile idiopathic arthritis; P-JIA, polyarticular juvenile idiopathic arthritis; PsA, psoriatic arthritis; sDMARDs, synthetic DMARDs; SD, standard deviation; S-JIA, systemic juvenile idiopathic arthritis.

were observed in pregnancies exposed to etanercept, with a median time to treatment discontinuation after conception of 41 days. Patients with active disease received oral steroids and underwent intra-articular glucocorticoid injections.

DAS28-CRP levels remained stable from preconception through gT1, but increased significantly in gT2 (+1.1, 95% confidence interval [CI]: 1.01 to 1.27, $p = 0.027$), and decreased – although not significantly – in the third trimester (gT3, Figure 1). Preconceptional DAS28-CRP and number of bDMARDs were the two significant determinants of the fluctuation of disease activity during gestation ($p = 0.005$ and 0.034, respectively, Supplementary Table 1). Age at onset, length of exposure to bDMARDs, and treatment with prednisone >7.5 mg were inserted as confounders. The number of preconceptional sDMARDs was not included because it did not contribute to the model.

Pregnancy outcome

As presented in Table 2, six pregnancies (12.2%) were electively terminated because of personal reasons (three cases), peri-conceptional exposure to MTX (two cases), or due to foetal trisomy 21 (one case). Excluding the electively terminated pregnancies, PrL occurred in six cases during gT1, all in women with oligoarthritis. In five of these six pregnancies, disease at conception was in remission; in one case, disease was in moderate activity at conception (DAS28-CRP 3.91). Two patients experienced a flare after PrL.

JIA women had a PrL probability of 13.9%, similar to the probabilities of 24.5% and 12.7% observed in SARD women and HCs (odds ratio [OR]: 0.87; 95% CI: 0.26 to 2.56; $p = 1.00$ and OR: 0.51; 95% CI: 0.17 to 1.27; $p = 0.18$, respectively); 86% pregnancies (37/43) culminated in a live birth; pre-eclampsia presented in one case (2.7%). Pre-eclampsia rate was similar to HCs (2.3%) and SARD women (1.3%). Two cases of placental detachment were reported; in one case leading to neonatal distress requiring access to neonatal intensive care unit.

Preterm delivery complicated 16.2% of JIA pregnancies, a figure higher than the probability of 5.2% and 4.6% observed in HCs and SARD women (OR: 3.01, 95% CI: 0.83 to 10.21, $p = 0.083$ and OR: 3.45, 95% CI: 1.05 to 9.82, $p = 0.02$, respectively).

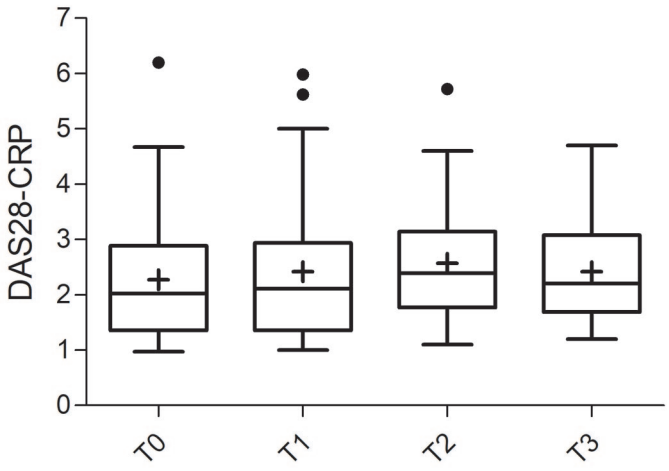

Figure 1. Fluctuation of disease activity evaluated by DAS28-CRP before and during pregnancy.
T0: conception; T1: first trimester of gestation; T2: second trimester of gestation; T3: third trimester of gestation. Boxes extend from the 25th to the 75th percentile of each group's distribution of values; within each box, horizontal lines correspond to median values. Whiskers were drawn based on Tukey method. Dots denote outlier values.

Table 2. Pregnancy outcome, complications, delivery, and neonatal features by disease category.

All pregnancies	**O-JIA (*n* = 29)**	**P-JIA (*n* = 10)**	**PsA + ERA (*n* = 7)**	**S-JIA (*n* = 3)**	**Total cohort (*n* = 49)**
DAS28-CRP at conception, mean (SD)	2.1 (0.8)	2.4 (1.3)	3.0 (1.7)	2.2 (0.9)	2.3 (1.1)
Miscarriage, % (*n*)	20.7 (6)	0.0 (0)	0.0 (0)	0.0 (0)	12.2 (6)
Elective termination, % (*n*)	10.3 (3)	10.0 (1)	14.3 (1)	33.3 (1)	12.2 (6)
Live birth pregnancies	*n* = 20	*n* = 9	*n* = 6	*n* = 2	*n* = 37
Gestational week at delivery, median (IQR)	38 (2.0)	39 (1.0)	39 (2.3)	39 (1.0)	39 (2.3)
Preterm delivery <37 gw, % (*n*)	10.0 (2)	11.1 (1)	16.7 (1)	0.0 (0)	10.8 (4)
Preterm delivery <34 gw, % (*n*)	5 (1)	0.0 (0)	0.0 (0)	0.0 (0)	2.7 (1)
Preterm delivery <32 gw, % (*n*)	0.0 (0)	0.0 (0)	16.7 (1)	0.0 (0)	2.7 (1)
Caesarean section, % (*n*)	65 (13)	33.3 (3)	83.3 (5)	100.0 (2)	67.6 (25)
Birth weight, grams, median (IQR)	3115 (572)	3100 (380)	3342 (1186)	3030 (80)	3.110 (470)
SGA, % (*n*)	0.0 (0)	11.1 (1)	0.0 (0)	0.0 (0)	2.7 (1)

Women with PrM displayed a more refractory disease compared with patients with successful pregnancy outcome, as documented by the requirement of a higher number of sDMARDs and bDMARDs (Table 3). In the GEE model, the number of bDMARDs and the length of the exposure to biologics in pregnancy significantly predicted PrM (Supplementary Table 2). Indeed, PrM probability increased with the number of preconceptional bDMARDs needed to obtain disease control ($p < 0.001$), while a longer treatment with bDMARDs after conception protected against PrM ($p = 0.018$). In particular, treatment with bDMARDs lasting at least 5 gw allowed a 50% reduction of PrM risk. Age at onset, treatment with prednisone >7.5 mg, ANA positivity,

Table 3. Demographic, clinical characteristics, and medication use during pregnancy and conception in pregnancies with and without PrM.

	Pregnancies with PrM (*n* = 12)	**Pregnancies without PrM (*n* = 30)**
Age at conception, mean (SD)	29.7 (2.9)	31.4 (5.3)
Age at JIA onset, median (IQR)	4.0 (10.5)	6.0 (9.2)
JIA category		
O-JIA	75.0 (9)	53.3 (16)
P-JIA	8.3 (1)	26.7 (8)
PsA + ERA	16.7 (2)	13.3 (4)
S-JIA	0.0 (0)	6.7 (2)
Disease duration in years, median (IQR)	21.0 (8.5)	23.0 (9.5)
ANA positivity, % (n)	58.3 (7)	53.3 (16)
Iridocyclitis, % (n)	33.3 (4)	26.7 (8)
DAS28-CRP, mean (SD)		
Preconception period	2.58 (1.51)	2.17 (0.99)
First trimester	3.02 (1.62)	2.12 (1.01)
No. of preconceptional sDMARDs, median (IQR)	3.0 (0.3)	2.0 (2.0)
No. of preconceptional bDMARDs, mean (SD)	2.5 (1.3)	2.0 (1.0)
bDMARD exposure from conception (days), median (IQR)	38.5 (13.8)	42.0 (36.0)
Prednisone >7.5 mg/day, % (n/N)		
First trimester	16.7 (2/10)	6.7 (2/30)
Second trimester	25.0 (2/8)	6.7 (2/30)
Third trimester	28.6 (2/7)	13.0 (3/23)
Prednisone dose (mg), median (IQR) (n/N)		
First trimester	7.5 (7.5)	0.0 (4.4)
Second trimester	7.5 (7.5)	0.0 (5.0)
Third trimester	7.5 (7.5)	2.5 (7.5)
No. of pregnancies on prednisone (n/N)		
First trimester	5/10	10/30
Second trimester	4/8	11/30
Third trimester	4/7	12/23

ANA, antinuclear antibodies; bDMARDs, biological disease modifying antirheumatic drugs; ERA, enthesitis-related arthritis; O-JIA, oligoarticular juvenile idiopathic arthritis; P-JIA, polyarticular juvenile idiopathic arthritis; PrM, pregnancy morbidity; PsA, psoriatic arthritis; sDMARDs, synthetic disease modifying antirheumatic drugs; S-JIA, systemic juvenile idiopathic arthritis arthritis.
Pregnancy morbidity was defined as unexplained spontaneous abortion before 10 gestational weeks; unexplained spontaneous abortion at or beyond 10 gw; premature delivery of a morphologically normal neonate before 37 gestational weeks.
Data relate to the 42 pregnancies that were considered in the generalized estimating equation model to measure the risk of pregnancy morbidity. Six pregnancies were not considered in the model because were electively terminated. One pregnancy was excluded because data about gestational week at delivery were missing.

and iridocyclitis were retained as confounders. Disease activity in gT1 and the number of preconceptional sDMARDs were not considered in the final model since they did not contribute to its fit ($p = 0.0115$, $p = 0.842$, $p = 0.466$, and $p = 0.858$, respectively).

Two patients required instrumental delivery (5.4%); caesarean sections were performed in 25 cases (67.6%), with hip endoprosthesis as the main indication. JIA women underwent C-section significantly more frequently compared to HCs and women with SARDs (OR: 14.14, 95% CI: 6.00 to 34.81, $p < 0.0001$ and OR: 9.33, 95% CI: 4.51 to 19.77, $p < 0.001$, respectively), who had a probability of caesarean of 9.2% and 15.6%, respectively.

Neonatal outcome

Among the 37 live births, one newborn presented a cleft palate, classified as major congenital anomaly (2.7%); the mother had a 6-week postconceptional exposure to golimumab. Another infant was diagnosed with inherited phenylketonuria at birth. This does not differ from data in the general population. One newborn (2.7%) was SGA, and the mother had low disease activity throughout pregnancy. The SGA rate in JIA patients was not dissimilar from the rate in HCs (2%). No major early or late complication, including infections, was observed in newborns of JIA mothers. Most infants (56%) were breastfed.

Disease activity in the postpartum period

Biological treatment was resumed in the postpartum period in 28 cases, at a median time of 16 weeks from delivery. All women were started on the same bDMARD received at the time of conception. In particular, bDMARD therapy was resumed shortly after delivery in 23 of the 37 pregnancies culminating with a live birth (62.2%), at a median time of 12 weeks from delivery. One patient was started on bDMARDs immediately after delivery because of moderate disease activity (DAS28-CRP 3.9). In addition, five more patients were started on bDMARDs at 9 or more months from delivery. In the first and second trimesters postpartum (ppT1 and ppT2), disease was not satisfactorily controlled in 12 cases (32.4%), always with a moderate disease activity. From 6 to 12 months after delivery, five women had a moderate disease activity (13.5%). Postpartum flares occurred in 14 out of 37 deliveries (37.8%): 7 in ppT1 (50%), 5 in ppT2 (35.7%) and 2 after 6 months from delivery (14.3%). Flares occurred more frequently in women with psoriatic and enthesitis-related arthritis (3/6 pregnancies) and in women with oligoarthritis (9/20 pregnancies).

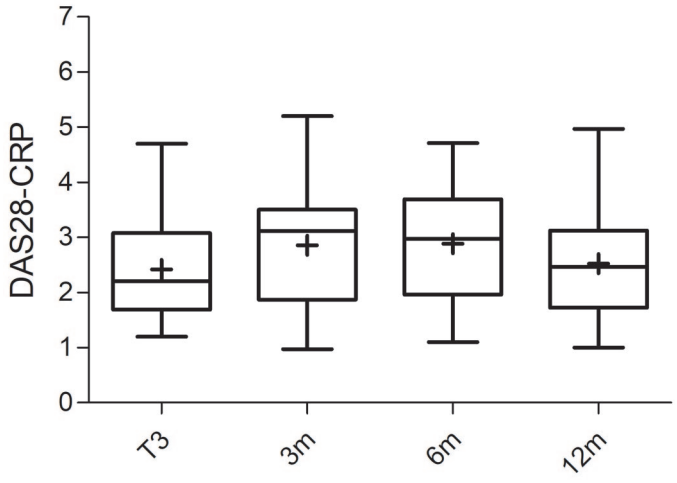

Figure 2. Fluctuation of disease activity evaluated by DAS28-CRP in the third trimester of pregnancy and in the year after delivery.
T3: third trimester of gestation; 3 m: 3 months postpartum; 6 m: 6 months postpartum; 12 m: 12 months postpartum. Boxes extend from the 25th to the 75th percentile of each group's distribution of values; within each box, horizontal lines correspond to median values. Whiskers were drawn based on Tukey method.

Adjusting estimates for breastfeeding and DAS28-CRP score in gT3, exposure to bDMARDs was the only determinant of postpartum disease activity (Supplementary Table 3). Disease activity peaked at ppT1, being significantly higher than in gT3 (+0.46; 95% CI: 0.01 to 0.92; $p = 0.048$); it stabilized at ppT2 to decrease at 1 year, although not significantly (*versus* gT3 −0.38; 95% CI: −0.86 to 0.10, Figure 2). In particular, in women starting bDMARDs within ppT1, a 23% decrease in DAS28-CRP scores was registered at ppT2 (*versus* ppT1: −0.70; 95% CI: −1.40 to 0.01; $p = 0.048$). When bDMARDs were started between 3 and 6 months after delivery, disease improved at 12 months, although not significantly (*versus* 6 months: −0.78; 95% CI: −2.25 to 0.69). Conversely, in case of bDMARD introduction after 6 months, disease activity increased at 6 months after delivery (*versus* ppT1: +0.32; 95% CI: −0.39 to 1.03) with a significant improvement at one year (*versus* ppT2: −1.02; 95% CI: −1.70 to −0.34).

Discussion

To our knowledge, this is the first study evaluating the fluctuation of disease activity during

pregnancy and in the postpartum period in women with JIA carefully accounting for all the potentially implicated clinical features. Importantly, disease activity was evaluated by means of DAS28-CRP, which is a validated measure in pregnant women.[21] The analysis of fluctuation of adequately corrected DAS28-CRP scores found a stable disease activity in gT1, a significant increase in gT2 then a reduction in gT3. Of note, the increase of 1.1 point in DAS28-CRP scores from gT1 to gT2 is relevant even from a clinical perspective. This observation is in partial agreement with previous recent studies, which showed that disease activity in JIA remains substantially stable throughout pregnancy but can register a not significant improvement in gT1 and a subsequent deterioration in gT2.[8,12,13] The discrepancy might be ascribed to the handling of raw data, which in previous studies were not corrected or corrected only for steroid and sulfasalazine use. The pattern of JIA disease activity described in modern rheumatology is very different from earliest studies, which reported disease activity amelioration during gestation.[1,10] We think that it is not appropriate to compare historical cohorts with recent data, due to the drastic changes in JIA management before and during gestation.

This study also allowed the identification of disease severity (number of preconceptional bDMARDs) and disease activity (DAS28-CRP scores) before conception as determinants of disease activity during pregnancy, highlighting the pivotal importance of a careful family planning even in the setting of JIA. Importantly, the length of exposure to biologics during pregnancy was not significantly associated with gestational disease activity. Such observation is consistent with the recent evidence, raised in 397 women with rheumatoid arthritis (RA) and 93 with JIA, that disease activity remained stable despite the discontinuation of TNF-α inhibitors before 20 gw, even though at univariate analysis women receiving TNF-α blockers beyond 20 gw were more likely to experience improved disease activity scores in gT3.[22] However, in our study, the duration of treatment with bDMARDs during gestation emerged, together with the number of preconceptional bDMARDs, as a significant predictor of pregnancy complications: the longer the patient continued treatment, the lower the probability of experiencing an adverse pregnancy outcome. Differently from other rheumatologic conditions, disease activity in pregnant JIA women did not predict a subsequent pregnancy complication in our model. This is consistent with the observation of Smith, who reported significance association between disease activity and preterm birth in RA but not in JIA.[6] However, it should not be concluded that disease activity in JIA does not impact PrM: biological treatment conditions DAS28-CRP scores, preventing a correct evaluation of the association of disease activity with PrM. Thus, inserting in the model disease activity would have led to a biased estimate of the direct effect of bDMARDs.[23] Women with PrM received more frequently steroids and at higher dose compared with women with uncomplicated pregnancies. However, the use of steroids during pregnancy at a daily dose above 7.5 mg was not identified as a significant predictor of PrM. This finding might be surprising given the well characterized role of steroids, especially if administered during the second and third trimesters, in inducing premature birth and other complications such as gestational hypertension, diabetes and infections. However, such association is dose-dependent, and in our cohort prednisone was never prescribed over 25 mg daily. At this dosage, prednisone is metabolized by the placenta to a relatively inactive metabolite, and only 10% crosses into the foetal circulation.[24]

Similarly, the sooner bDMARDs are reintroduced after delivery, the sooner disease control is obtained. In particular, the mixed linear model clearly documented that disease activity tended to rise in the postpartum period compared with gT3. Indeed, DAS28-CRP scores were significantly higher in ppT1, and remained stable in ppT2 with a significant decrease at 1 year. Such trend has also been reported in two studies analysing postpartum disease activity in JIA women.[12,13] Correcting data only for steroids and sulfasalazine exposure, Ursin observed a peak of disease activity at 6 weeks from delivery, similar to Garcia-Fernandez.[12,13] Worsening of disease activity following delivery in women with JIA has been already known, even though earliest reports showed a different trend, with a peak of disease activity in the second and third trimesters after delivery.[1,10]

Analysis of the fluctuation of postpartum disease activity might highlight a detrimental effect of lactation: an earlier study suggested that breastfeeding JIA mothers were more prone to disease flare, and postulated that the pro-inflammatory hormone prolactin might be implicated.[10] However, our model showed that the deleterious impact of

breastfeeding was fictitious, unmasking the consequence of delaying the resume of bDMARDs: breastfeeding mothers were started on biologics approximately 2 months later.

When evaluating disease activity after delivery, it is important to note that in our data set the rate of missing data was not negligible: DAS28-CRP at 3 months postpartum was not available for six pregnancies, while data at 6 as well as 12 months had not been collected in nine pregnancies. Such rate of missing data might have biased the reliability of our results, leading to an overestimation of disease activity in the postpartum period. Indeed, we might have missed patients that, due to a good control of disease activity in the first year after delivery, had not sought medical advice.

Potential differences among JIA categories in disease course during and after pregnancy have been seldom investigated. In our cohort, gestational flares presented mostly in women with psoriatic arthritis. This observation is in agreement with what reported by Drechsel, whereas Garcia-Fernandez described flares only in pregnant women with oligoarticular and polyarticular JIA.[8,13] In our cohort, the rate of disease flare in the postpartum period doubled the figure observed during pregnancy (38% *versus* 16%), being most common in women with enthesitis-related arthritis and psoriatic arthritis, whereas Garcia-Fernandez reported more flares in new mothers with oligoarthritis.[13] Available evidence is too limited to draw any conclusion on a potentially different behaviour of JIA categories during and after pregnancy.

In this study, PrL prevalence among JIA women was similar to HCs and SARD women, in agreement with the few previous studies.[8,10,13] In two cases, pregnancies were electively terminated due to concerns of ongoing MTX.[25] The only patient exposed to leflunomide at conception did not experience any major obstetric or neonatal complications.[26] Importantly, we observed an increased rate of premature births, with an estimated probability of 16.2%. This finding is consistent with most literature, as many reports described an increased incidence of prematurity.[2–8] Available evidence is still conflicting, as other authors denied this association.[9,10] Our JIA patients presented a rate of pre-eclampsia at any gestational age not higher than HCs and women with SARDs. Even though most authors describe an increased risk of pre-eclampsia in JIA pregnancies compared to the general population, our observation has been reported also by others.[2,5,6,9,27]

Caesarean section was very common in our JIA patients, with a probability of 67.6%. This figure was significantly higher than both healthy and disease controls, and might be partially explained by concerns about parturition stress on hip prosthesis. C-section was reported as the preferred birth modality in JIA back in 1991; however, the rate of caesareans in our cohort is to date the highest described: in previous literature, caesarean sections were performed from 8.6% to 51% of cases.[1,2,5,6,8–10,27] In this regard, it should be highlighted that the rate of caesarean section in Italian general population is 38%.[28]

There is no consensus about the potential increased risk of SGA in JIA: few reports deny an increased rate, while most claim a raise of SGA probability among newborns to JIA mothers.[2–5,8–10] In our cohort, the prevalence of SGA was 2.7%, a figure that is within the expected range in the Italian population (7.6%).[29]

Notwithstanding the long exposure to DMARDs, the present study does not describe an increased risk of major neonatal malformations compared with the general population. The rate of neonatal malformation was 2.7%, similar to the 2% reported in the online European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT). This finding confirms previous reports,[8,9] concordant in denying the 9% risk of congenital malformations described by Feldmann, mostly consisting in heart and neural tube defects.[3] Noteworthy, the latter study was based on a National registry, where the lack of details about drug exposure and other potential causes of congenital anomalies impinges the attribution of such increased risk of malformation to JIA itself.

Limitations of the present study include its retrospective design and the limited sample size, which prevented further statistical analysis of less common outcomes. However, all pregnancies were observed over a 20-year period in a single institution, allowing a careful collection of clinical data, and followed up in a dedicated joint rheumatology/obstetrics clinic. To optimize the estimate of obstetric and foetal complications, data from both healthy and disease controls were included

as comparison groups. A sophisticated statistical approach allowed us to account that pregnancies in a single woman are distinct yet correlated events and to analyse gestational and postpartum fluctuation of disease activity as well as PrM occurrence carefully accounting for the full range of control variables. Due to the low prevalence, well-characterized risk factors of PrM such as diabetes, obesity, tobacco use, and aPL positivity were not considered in the statistical analysis. In addition, our cohort included exclusively women with JIA persisting into adulthood, implying that our results cannot be extrapolated to the whole JIA population. Indeed, in a minority of JIA cases, disease remission without any treatment can be achieved before entering the adult age. In these patients, the inflammatory and treatment loads are much less burdensome, and this might result in a better pregnancy outcome.

In conclusion, our data offer several novel insights into reproductive aspects of JIA. A fluctuation pattern of disease activity in JIA, accounting for all potentially relevant variables, has been drawn for the first time during pregnancy and postpartum period. According to our models, disease activity in JIA significantly increases both during pregnancy, peaking in gT2, and after delivery, with the highest scores being registered at ppT1. Our data confirmed that JIA women are more likely to deliver preterm and by caesarean section, whereas the risk of PrL, pre-eclampsia, SGA and congenital anomalies is not increased. Our observations display also therapeutic implications, which clinicians should take into account whenever evaluating the management options in JIA pregnant women. Indeed, if treatment with bDMARDs during pregnancy did not impact disease activity, it reduced the risk of PrM. In addition, prompt institution of bDMARDs after delivery allowed to obtain disease control earlier, with important clinical and socioeconomic consequences.

In a recent survey, pregnancy and childbirth emerged among the most urgent information that JIA patients in transitional age wish to receive:[30] hopefully these data will allow optimizing the reproduction counselling that rheumatologists offer to JIA women in childbearing years.

Author contributions

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Ethics statement

This study complies with the Declaration of Helsinki. The local ethics committee approved the study (Comitato Etico Milano Area B, Milan, Italy; authorization 629_2017bis – PROMAMMA study obtained on 24 October 2017). Informed consent was not obtained from participating subjects due to the retrospective design.

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Supplemental material

Supplemental material for this article is available online.

References

1. Ostensen M. Pregnancy in patients with a history of juvenile rheumatoid arthritis. *Arthritis Rheum* 1991; 34: 881–887.
2. Chen JS, Ford JB, Roberts CL, *et al*. Pregnancy outcomes in women with juvenile idiopathic arthritis: a population-based study. *Rheumatology (Oxford)* 2013; 52: 1119–1125.
3. Ehrmann Feldman D, Vinet É, Bernatsky S, *et al*. Birth outcomes in women with a history of juvenile idiopathic arthritis. *J Rheumatol* 2016; 43: 804–809.
4. Mohamed MA, Goldman C, El-Dib M, *et al*. Maternal juvenile rheumatoid arthritis may be associated with preterm birth but not poor fetal growth. *J Perinatol* 2016; 36: 268–271.
5. Remaeus K, Johansson K, Askling J, *et al*. Juvenile onset arthritis and pregnancy outcome: a population-based cohort study. *Ann Rheum Dis* 2017; 76: 1809–1814.
6. Smith CJF, Förger F, Bandoli G, *et al*. Factors associated with preterm delivery among women with rheumatoid arthritis and women with juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)* 2019; 71: 1019–1027.
7. Kolstad KD, Mayo JA, Chung L, *et al*. Preterm birth phenotypes in women with autoimmune rheumatic diseases: a population-based cohort study. *BJOG* 2020; 127: 70–78.
8. Drechsel P, Stüdemann K, Niewerth M, *et al*. Pregnancy outcomes in DMARD-exposed patients with juvenile idiopathic arthritis-results from a JIA biologic registry. *Rheumatology (Oxford)* 2020; 59: 603–612.
9. Zhang-Jian SJ, Yang HY, Chiu MJ, *et al*. Pregnancy outcomes and perinatal complications of Asian mothers with juvenile idiopathic arthritis – a case-control registry study. *Pediatr Rheumatol Online J* 2020; 18: 9.
10. Musiej-Nowakowska E and Ploski R. Pregnancy and early onset pauciarticular juvenile chronic arthritis. *Ann Rheum Dis* 1999; 58: 475–480.
11. Förger F and Villiger P. Immunological adaptations in pregnancy that modulate rheumatoid arthritis disease activity. *Nature Rev* 2000; 16: 113–122.
12. Ursin K, Lydersen S, Skomsvoll JF, *et al*. Disease activity of juvenile idiopathic arthritis during and after pregnancy: a prospective multicenter study. *J Rheumatol* 2018; 45: 257–265.
13. García-Fernández A, Gerardi MC, Crisafulli F, *et al*. Disease course and obstetric outcomes of pregnancies in juvenile idiopathic arthritis: are there any differences among disease subtypes? A single-centre retrospective study of prospectively followed pregnancies in a dedicated pregnancy clinic. *Clin Rheumatol* 2021; 40: 239–244.
14. Andreoli L, Gerardi MC, Fernandes M, *et al*. Disease activity assessment of rheumatic diseases during pregnancy: a comprehensive review of indices used in clinical studies. *Autoimmun Rev* 2019; 18: 164–176.
15. Nigrovic PA, Colbert RA, Holers VM, *et al*. Biological classification of childhood arthritis: roadmap to a molecular nomenclature. *Nat Rev Rheumatol* 2021; 17: 257–269.
16. Petty RE, Southwood TR, Manners P, *et al*. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004; 31: 390–392.
17. van Gestel AM, Prevoo ML, van 't Hof MA, *et al*. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. *Arthritis Rheum* 1996; 39: 34–40.
18. von Elm E, Altman DG, Egger M, *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med* 2007; 4: e296.
19. Chighizola CB, Gerosa M, Trespidi L, *et al*. Update on the current recommendations and outcomes in pregnant women with antiphospholipid syndrome. *Expert Rev Clin Immunol* 2014; 10: 1505–1517.
20. Skorpen CG, Hoeltzenbein M, Tincani A, *et al*. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis* 2016; 75: 795–810.
21. de Man YA, Hazes JM, van de Geijn FE, *et al*. Measuring disease activity and functionality during pregnancy in patients with rheumatoid arthritis. *Arthritis Rheum* 2007; 57: 716–722.
22. Förger F, Bandoli G, Luo Y, *et al*. No association of discontinuing tumor necrosis factor inhibitors before gestational week twenty in well-controlled rheumatoid arthritis and juvenile idiopathic arthritis with a disease worsening in late pregnancy. *Arthritis Rheumatol* 2019; 71: 901–907.
23. Pearl J. *Causality: models, reasoning, and inference*. Cambridge: Cambridge University Press, 2009.

24. Benediktsson R, Calder AA, Edwards CR, *et al*. Placental 11 beta-hydroxysteroid dehydrogenase: a key regulator of fetal glucocorticoid exposure. *Clin Endocrinol (Oxf)* 1997; 46: 161–166.

25. Weber-Schoendorfer C, Chambers C, Wacker E, *et al*. Pregnancy outcome after methotrexate treatment for rheumatic disease prior to or during early pregnancy: a prospective multicenter cohort study. *Arthritis Rheumatol* 2014; 66: 1101–1110.

26. Weber-Schoendorfer C, Beck E, Tissen-Diabaté T, *et al*. Leflunomide – a human teratogen? A still not answered question. An evaluation of the German Embryotox pharmacovigilance database. *Reprod Toxicol* 2017; 71: 101–107.

27. Feldman DE, Vinet É, Bérard A, *et al*. Heart disease, hypertension, gestational diabetes mellitus, and preeclampsia/eclampsia in mothers with juvenile arthritis: a nested case-control study. *Arthritis Care Res (Hoboken)* 2017; 69: 306–309.

28. Macfarlane AJ, Blondel B, Mohangoo AD, *et al*.; Euro-Peristat Scientific Committee. Wide differences in mode of delivery within Europe: risk-stratified analyses of aggregated routine data from the Euro-Peristat study. *BJOG* 2016; 123: 559–568.

29. Chiavaroli V, Castorani V, Guidone P, *et al*. Incidence of infants born small- and large-for-gestational-age in an Italian cohort over a 20-year period and associated risk factors. *Ital J Pediatr* 2016; 42: 42.

30. Matsumoto T and Mori M. Questionnaire survey on transitional care for patients with juvenile idiopathic arthritis (JIA) and families. *Mod Rheumatol* 2021; 31: 691–696.