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Safety of biologic immunosuppressants in pregnant women with immune-mediated inflammatory diseases

Martínez-Sánchez N [a,*], J. Álvarez-Troncoso [b], Á. Robles-Marhuenda [b], M. De la Calle Fernández-Miranda [a], M.L. Muner Hernando [a], J.L. Bartha [a]

[a] Servicio de Ginecología y Obstetricia, Unidad de Embarazo de Alto Riesgo, Hospital Universitario La Paz, Spain
[b] Servicio de Medicina Interna, Unidad de Enfermedades Autoinmunes Sistémicas, Hospital Universitario La Paz, Spain

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ABSTRACT

Background: Immune-mediated inflammatory diseases (IMIDs) typically affect women of childbearing age. One of the challenges in treating these women during pregnancy is to manage the disease while minimizing or avoiding the use of disease-modifying antirheumatic drugs (DMARDs) that may increase the risk to the mother or fetus. Biologic therapy has transformed the management of these patients. This study aimed to evaluate the maternal-fetal safety and perinatal outcomes in pregnant women with IMID exposed to biologic DMARDs either pre-conceptionally or during pregnancy and compare them with women using conventional DMARDs and a group of healthy pregnant women.

Methods: We conducted a retrospective study with prospective follow-up of pregnant women with IMID at a single center. We analyzed baseline maternal demographic characteristics, diseases, DMARDs, and maternal-fetal outcomes.

Results: A cohort of 244 pregnancies was studied. One hundred twenty-eight patients met classificatory criteria for rheumatic and musculoskeletal diseases (RMD) or inflammatory bowel disease (IBD), and 116 pregnancies of healthy women were evaluated from the same study period. One hundred and one pregnancies in IMID patients (89.84 %) occurred under immunosuppressive treatment, 78.91 % of IMID pregnancies were under cDMARD (33.59 % exclusive cDMARD), 56.25 % under bDMARD, and 27.34 % under oral glucocorticoids. Anti-TNF was the most frequent (88.88 %) bDMARD and was used in 50.78 % of the IMIDs. There was at least one flare in 37.10 % of the IMID pregnancies, and 9.38 % experienced more than one. Among flares, 43.48 % happened in the first trimester, 34.78 % in the second trimester, and 19.57 % in the third. Flares were more frequent in the RMD patients compared with IBD ($p = 0.041$; OR 2.15, 95%CI: 1.03–4.52). Flare was associated with discontinuation of bDMARD before the eighth week of gestation ($p = 0.016$), but especially in the second ($p = 0.042$) and third trimester ($p = 0.012$). Maternal infections were an infrequent complication overall (7.66 %), although more frequent in patients with IMIDs ($p = 0.004$) but were not associated with cDMARD or bDMARD. IMID patients needed assisted reproductive techniques (ART) more often ($p = 0.001$, OR 2.83, 95%CI: 1.02–7.90). More cesarean sections were performed in gestations under treatment with bDMARD ($p = 0.020$) and especially in those under treatment with anti-TNF. Aneuploidies calculation risk and fetal malformations were not correlated with DMARDs (cDMARDs, bDMARDs, or its combination) nor with any of the DMARDs individually pre-concepcionally or during gestation. Small for gestational age (SGA) newborns were higher in patients with IMIDs however, it was not associated with DMARD use.

Discussion: In general, patients with IMIDs who require treatment with bDMARDs have a more severe or refractory disease prior to gestation. In our cohort, we found a higher risk of flare among patients with bDMARDs, especially when those were suspended early. Among maternal outcomes, we found that IMID patients needed ART more often. This is probably, first of all, because of maternal age. Among fetal outcomes, there are no differences in congenital malformations in the IMIDs and healthy patients and were not correlated with DMARDs.

Conclusion: The use of bDMARDs was effective in disease control and safe from a maternal-fetal point of view, with no increase in prematurity, SGA, malformations, or infections.

* Corresponding author. Hospital Universitario La Paz Paseo de la Castellana, 261, 28046, Madrid, Spain.
E-mail address: doctora.martinezsanchez@gmail.com (M.-S. N).

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1. Background

Immune-Mediated Inflammatory Diseases (IMID) usually affect women of childbearing age [1–3]. Thus, treating such disorders in women during pregnancy is essential to their management. Besides, half of the patients with inflammatory bowel disease (IBD) and rheumatic and musculoskeletal diseases (RMD) debut in this period [4,5]. Pregnant women with IBD have an increased risk of complications like spontaneous abortion, preterm birth, need for cesarean delivery, and low birth weight [4]. Also, almost 2 out of 5 patients with RMD present some maternal-fetal complication during gestation [5].

When considering treatment options, a challenge of treating women during pregnancy is to keep the disease under control while minimizing or avoiding Disease-Modifying Antirheumatic Drugs (DMARD) that may increase maternal or fetal risk. The relative benefits and risks to the mother and fetus of using a particular medication to maintain disease control or to treat active disease during pregnancy depend upon the specific clinical context and may be influenced by gestational age and other factors. Importantly, the untreated disease carries risks to the mother and the developing fetus [6].

Biologic therapy has changed the management of patients with RMD and IBD [6–8]. It has provided clinical stability for women who had not considered pregnancy, both due to the contraindication of some classical DMARDS (cDMARDs) during pregnancy and the possible worsening of the disease. Biologic DMARDs (bDMARDs) target specific molecules, cells, and pathways that cause inflammation and tissue damage [6–8].

Among bDMARDs, the greatest experience is with tumor necrosis factor inhibitors (anti-TNF) [8]. Although it is increasing, the different guidelines for managing different IMIDs do not have a clear consensus, especially when withdrawing the bDMARD, thus reducing the theoretical harmful effects on the fetus and the newborn without increasing complications in the mother [6–12].

This study aimed to evaluate the maternal-fetal safety and perinatal outcomes in pregnant women with IMID (exposed preconcepcionally or during pregnancy to bDMARDs) and compare them with women with cDMARDs and a group of healthy pregnant women.

2. Methods

2.1. Study population

We conducted a retrospective study with prospective follow-up of pregnant women with Immune-Mediated Inflammatory Diseases (IMID) between 2011 and 2021 at the Autoimmune Diseases and Pregnancy Clinic of Hospital Universitario La Paz, which is a Spanish Public Hospital and a National Reference Center for Systemic Autoimmune Diseases. The study was conducted as a single-center study. Approximately 150 newly pregnant women with Lupus, Antiphospholipid Syndrome, Sjögren, and other IMID are seen annually at the High-Risk Pregnancy Clinic.

All pregnant women with IMID under bDMARD were included, as were consecutive cases of IBD, RMD, and healthy matched controls in the selected period. Baseline demographic characteristics, smoking status, parity, and previous abortions were recorded for healthy and IMID patients. Clinical and analytical data were extracted from the electronic medical records of patients under follow-up in the High-Risk Pregnancy Clinic. For patients with IMID, we evaluated pregestational and gestational immunosuppressive therapies, years of disease evolution, and flare history before, during, or after gestation. Flare was defined as worsening clinical or serological activity, as well as patient-reported disease activity requiring starting or increasing medication.

We performed a multivariate analysis to assess the effect of different immunosuppressants (cDMARD and bDMARD) on maternal (gestational age, induction of labor, type of delivery, the reason for cesarean section, preeclampsia, maternal infections), perinatal (calculation risk of chromosomal abnormalities, congenital malformations, prematurity, small for gestational age (SGA) fetus, or intrauterine growth restriction (IUGR) [13], preeclampsia, need for labor induction, cesarean section, maternal

Table 1
Demographic and preconceptional data in healthy and IMID pregnancies.

	Healthy (n = 116)	IMID (n = 128)	p-value	RMD (n = 59)	IBD (n = 69)	p-value
Age (years)	31.49	34.48	**<0.001**	34.36	34.58	0.532
Height (cm)	166.14	163.59	**0.017**	164.53	162.97	0.160
Weight (kg)	65.01	61.48	**0.005**	65.07	58.96	**0.010**
BMI (kg/m2)	23.79	23.03	0.179	24.22	22.27	0.080
Time of disease (years)	–	9.00	–	9.24	8.81	0.906
Diabetes (%)	5.17 %	1.56 %	0.114	3.39 %	0.00 %	0.123
Hypo/hyperthyroidism (%)	11.21 %	16.41 %	0.242	16.95 %	15.94 %	0.878
Previous smoker (%)	18.10 %	19.53 %	0.776	13.56 %	24.64 %	**0.115**
Steroids (%)	–	27.34 %	–	38.98 %	17.39 %	**0.006**
DMARD (%)	–	89.84 %	–	81.36 %	97.10 %	**0.003**
cDMARD (%)	–	78.91 %	–	69.49 %	86.96 %	**0.016**
bDMARD (%)	–	56.25 %	–	61.02 %	52.17 %	0.315
cDMARD & bDMARD (%)	–	45.31 %	–	49.15 %	42.03 %	0.420
Methotrexate (previous) (%)	–	18.75 %	–	37.29 %	2.90 %	**<0.001**
Leflunomide (previous) (%)	–	3.12 %	–	6.78 %	0.00 %	**0.028**
Azathioprine (%)	–	25.78 %	–	3.39 %	43.48 %	**<0.001**
Hydroxychloroquine (%)	–	12.50 %	–	27.12 %	0.00 %	**<0.001**
Mesalazine (%)	–	28.91 %	–	0.00 %	53.62 %	**<0.001**
Sulfasalazine (%)	–	17.19 %	–	35.59 %	1.45 %	**<0.001**
anti-TNF (%)	–	50.78 %	–	50.85 %	50.72 %	0.989
Tocilizumab (%)	–	2.34 %	–	5.08 %	0.00 %	0.058
Rituximab (%)	–	2.34 %	–	5.08 %	0.00 %	0.058
Abatacept (%)	–	0.78 %	–	1.69 %	0.00 %	0.278
Parity (Nulliparous) (%)	67.86 %	71.65 %	0.555	70.69 %	72.46 %	0.825
Abortion (previous) (%)	25.27 %	32.28 %	0.262	36.21 %	28.99 %	0.386
bDMARD 1st trimester (%)	–	34.13 %	–	34.48 %	33.82 %	0.938
bDMARD 2nd trimester (%)	–	36.51 %	–	37.93 %	35.29 %	0.759
bDMARD 3rd trimester (%)	–	28.57 %	–	37.93 %	20.59 %	**0.032**
Last dose bDMARD (week)	–	29.47	–	28.65	30.46	0.204

BMI: body mass index; IMID: Immune-Mediated Inflammatory Diseases; RMD: Rheumatic and Musculoeskeletal Diseases; IBD: inflammatory bowel disease; DMARD: Disease-Modifying Antirheumatic Drugs; cDMARD: classic DMARD; bDMARD: biologic DMARD.

Table 2
Use of bDMARD during pregnancy.

bDMARD (n = 72)	Type of bDMARD	n (%)	RMD (n)	IBD (n)	Associated cDMARD (%)	Last-dose bDMARD (week)
Anti-TNF	**All anti-TNF**	**64 (88.88 %)**	**30**	**35**	**78.46 %**	**30,04**
	Certolizumab	19 (26.64 %)	18	1	63.16 %	34,21
	Adalimumab	19 (26.64 %)	4	15	78.95 %	32,00
	Infliximab	17 (23.61 %)	0	17	88.24 %	28,8
	Etanercept	9 (12.50 %)	8	1	88.89 %	18,00
Anti-CD20	**Rituximab**	**3 (4,17 %)**	**3**	**0**	**100 %**	**preconcepcional**
Anti-IL6	**Tocilizumab**	**3 (4.17 %)**	**3**	**0**	**100 %**	**preconcepcional**
Anti-CTLA4	**Abatacept**	**1 (1.39 %)**	**1**	**0**	**100 %**	**preconcepcional**
Anti-IL23	**Risankizumab**	**1 (1.39 %)**	**0**	**1**	**100 %**	**preconcepcional**

DMARD: Disease-Modifying Antirheumatic Drugs; cDMARD: classic DMARD; bDMARD: biologic DMARD.

infection), and newborn outcomes (gender, weight, Apgar score, arterial pH in umbilical cord, infection). We defined prematurity as delivery before 37 weeks gestation and SGA as a newborn weight below the 10th percentile. We diagnosed preeclampsia in the presence of hypertension and proteinuria [14].

This study complied with the Declaration of Helsinki and was approved by the Local Ethics Commission.

2.2. Statistic analysis

Clinical variables were described by frequencies and percentages (%) in the case of categorical variables, and means and standard deviations (SD) or medians and interquartile ranges (IR) in the case of continuous variables with normal or non-normal distribution, respectively. Qualitative variables were studied with the chi-square test to determine whether there was a statistically significant association. The odds ratio (OR) was calculated to measure association in cohort studies.

A multivariate analysis was performed using logistic regression in the statistical software Wizard Pro for Mac version 2.0.12. The variables included in the analysis were maternal age, gestational age at delivery, preterm labor, induction of labor, mode of delivery, hypertension, and maternal infections. Variable selection was performed using a stepwise approach, with variables being included in the final model if their p-value was less than 0.05. The odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated to assess the effect of each variable on the outcomes of interest.

3. Results

3.1. Demographic and preconceptional data

A cohort of 244 pregnancies was included in the study, consisting of 128 patients meeting the classificatory criteria for RMD or IBD according to updated classificatory criteria, and 116 pregnancies from healthy women during the same study period. The mean age of pregnant women was 33.05 years, with 70.14 % being nulliparous. The rest of the demographic data are detailed in Table 1. Of the 128 pregnancies with IMID, 63 had isolated IBD (classified as Crohn's disease (CD) or ulcerative colitis (UC)), and 59 had isolated RMD (classified as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and juvenile idiopathic arthritis (JIA)). Six patients also presented a RMD associated with IBD (5 AS and 1 PsA) but classified as IBD. Within IBD patients (n = 69), 39 pregnancies were in patients with Crohn's disease (CD) and 30 with ulcerative colitis (UC). Within RMDs (n = 65), 33 pregnancies were in patients with RA, 29 in AS, and 3 in PsA.

There were no differences in the percentage of previous pregnancies or miscarriages between the groups (Table 1). No factor associated with a higher risk of miscarriage was found in our cohort.

Table 3
Maternal and perinatal outcomes.

	Healthy (n = 116)	IMID (n = 128)	p-value	RMD (n = 59)	IBD (n = 69)	p-value	bDMARD (n = 72)	no bDMARD (n = 56)	p-value
Spontaneous conception (%)*	92.31 %	83.74 %	0.001	79.66 %	87.50 %	0.239	79.41 %	89.09 %	0.148
Flare (%)	–	37.10 %	–	46.55 %	28.79 %	0.041	44.44 %	26.92 %	0.046
>1 flare (%)	–	9.38 %	–	11.86 %	7.25 %	0.372	13.89 %	3.57 %	0.047
1st trimester flare (%)	–	16.13 %	–	17.24 %	15.15 %	0.752	16.67 %	15.38 %	0.848
2nd trimester flare (%)	–	18.55 %	–	27.59 %	10.61 %	0.015	25.00 %	9.62 %	0.030
3rd trimester flare (%)	–	7.26 %	–	10.34 %	4.55 %	0.214	9.72 %	3.85 %	0.213
Postpartum flare (%)	–	4.84 %	–	3.45 %	6.06 %	0.499	6.94 %	1.92 %	0.199
Miscarriage (%)	0 %	2.38 %	0.185	1.96 %	3.64 %	0.603	1.85 %	3.85 %	0.536
Pre-eclampsia (%)	2.04 %	3.54 %	0.514	5.77 %	1.64 %	0.236	4.41 %	2.22 %	0.537
MoM PAPPA (mean)	1.04	0.99	0.656	1.12	0.90	0.082	1.05	0.90	0.314
MoM βHCG (mean)	1.20	1.30	0.199	1.31	1.30	0.505	1.17	1.50	0.153
Gestational age <37 weeks (%)	9.48 %	9.38 %	0.977	3.39 %	14.49 %	0.032	9.72 %	8.93 %	0.879
Gestational age <34 weeks (%)	2.59 %	2.34 %	0.903	0 %	4.35 %	0.105	4.17 %	0 %	0.122
Need for labor induction (%)	30.10 %	42.00 %	0.077	46.67 %	38.18 %	0.392	39.66 %	45.24 %	0.577
Cesarean section (%)	26.92 %	32.17 %	0.396	30.19 %	33.87 %	0.673	40.91 %	20.41 %	0.020
Fetal percentile <10 % at birth (%)	6.03 %	17.19 %	0.007	20.34 %	14.49 %	0.382	16.67 %	17.86 %	0.859
Fetal percentile <3 % at birth (%)	3.45 %	7.81 %	0.143	10.17 %	5.80 %	0.358	8.33 %	7.14 %	0.803
APGAR 1 (mean)	8.64	8.55	0.741	8.62	8.50	0.282	8.45	8.69	0.571
APGAR 5 (mean)	9.51	9.52	0.701	9.65	9.42	0.138	9.42	9.55	0.380
Arterial pH at birth (mean)	7.28	7.27	0.849	7.27	7.27	0.981	7.27	7.28	0.753
Fetal malformations (%)	2.59 %	5.47 %	0.257	1.69 %	8.70 %	0.082	5.56 %	3.49 %	0.458
Maternal infections (%)	2.04 %	12.61 %	0.004	18.00 %	8.20 %	0.122	11.94 %	13.64 %	0.792
Newborn infections (%)	4.08 %	4.59 %	0.859	4.00 %	5.08 %	0.787	7.69 %	2.82 %	0.110

DMARD: Disease.

3.2. Use of DMARDs

One hundred and one pregnancies in patients with IMID (89.84 %) occurred while receiving immunosuppressive treatment. Of the IMID pregnancies, 78.91 % were treated with cDMARD, of which 33.59 % received exclusive cDMARD treatment. In addition, 56.25 % of the IMID pregnancies were treated with bDMARD and 27.34 % with oral glucocorticoids. A combination of cDMARD and bDMARD was used in 45.31 % of the patients. The most commonly used preconceptional cDMARDs were mesalazine (n = 37 pregnancies, all with IBD), azathioprine (n = 33, mostly IBD), methotrexate (n = 24), and sulfasalazine (n = 22). All pregnant women with previous methotrexate treatment discontinued it at least three months before conception, while the remaining cDMARDs were continued during gestation.

Among the bDMARDs, anti-tumor necrosis factor (anti-TNF) drugs were the most frequent (88.88 %) and used in 50.78 % of IMID pregnancies. Adalimumab and certolizumab were used in 19 gestations each, infliximab in 17, and etanercept in 9. There was no data on golimumab use in the cohort. Other bDMARDs used were rituximab (n = 3), tocilizumab (n = 3), abatacept (n = 1), and risankizumab (n = 1). All patients receiving bDMARD had started the drug before the onset of pregnancy, but in 3 cases, it was necessary to start it in the second trimester due to poor disease control. Only anti-TNFs were maintained during gestation (Table 2). Certolizumab was the anti-TNF maintained for the longest duration, followed by adalimumab. There was no significant difference in combination with cDMARD among the different anti-TNFs. Rituximab, tocilizumab, abatacept, and risankizumab were combined with cDMARD.

3.3. Maternal outcomes

There were significant differences in the percentage of spontaneous conception between healthy and patients with IMID. Patients with IMID required assisted reproductive techniques (ART) more frequently (p = 0.001, OR 2.83, 95%CI: 1.02–7.90) (Table 3).

In the IMID pregnancies, there was at least one flare in 37.10 % of cases, with 9.38 % experiencing more than one flare. Among flares, 43.48 % occurred in the first trimester, 34.78 % in the second trimester, and 19.57 % in the third. Flares were more frequent in patients with RMD compared to IBD (p = 0.041; OR 2.15, 95%CI: 1.03–4.52). In IBD patients, fecal calprotectin levels at the first visit after gestation were associated with the risk of any flare (p < 0.001), presenting >1 flare (p = 0.005), first-trimester flare (p < 0.001), second-trimester flare (p = 0.004), and postpartum flare (p = 0.006). In our cohort, fecal calprotectin levels >50 μg/g presented a positive predictive value of 74 % and a negative predictive value of 72 %. HLA-B27 positivity was associated with an increased risk of flare during pregnancy in ankylosing spondylitis (p = 0.016; OR 14.00, 95%CI: 1.20–163.37). Patients on bDMARD had a higher risk of flare (p = 0.046; OR 2.17, 95%CI: 1.01–4.69). On the other hand, patients who discontinued bDMARD before the eighth week of gestation had a higher risk of flare (p = 0.016), especially in the second (p = 0.042) and third trimesters (p = 0.012).

Maternal infections were an infrequent complication overall (7.66 %), although more frequent in patients with IMID (p = 0.004; OR 6.93, 95%CI: 1.53–31.31). Maternal infections occurred in the first (4.31 %) or third (2.39 %) trimester, being very rare in the second (0.48 %) and the postpartum period (0.48 %). Infections were urinary (37.50 %) or respiratory (37.50 %), and 93.75 % were mild and did not require hospitalization. Maternal infections were not associated with conventional cDMARD or bDMARD. However, they were associated with steroid use (p = 0.049). In the bDMARD subgroup, steroid use was associated with an increased risk of maternal infections (p < 0.001, OR 16.66, 95%CI: 2.89–95.97).

The rates of preeclampsia and labor induction were similar between pregnancies with IMIDs and those without. Approximately one-third (29.68 %) of all pregnancies (including those with and without IMIDs) ended with a cesarean section, with no significant differences observed between patients with RMD and IBD. Cesarean sections were not performed for maternal pathology in patients with RMD, and only two patients with IBD underwent cesarean section for this indication. More cesarean sections were performed in pregnancies under treatment with bDMARDs (p = 0.020), especially those receiving anti-TNF therapy (p = 0.023). The most common reasons for cesarean section were the risk of fetal well-being loss (38.81 %), breech presentation (22.39 %), failure of induction (16.42 %), non-progression of labor (13.43 %), and pelvicephalic disproportion (8.96 %). However, in pregnant women with IMIDs, the second most common reason after fetal well-being loss (45.95 %) was induction failure (27.03 %), with statistically significant differences observed (p = 0.009).

3.4. Fetal and newborn outcomes

An aneuploidy risk calculation was performed in the first trimester, and there were no significant differences between pregnancies with and without bDMARDs. Ten pregnancies (4.10 %) had congenital malformations, with no statistically significant differences observed between healthy women and those with IMIDs, or with the use of bDMARDs. Three cases of single umbilical artery (cord malformation) were found in the IMID subgroup, but no fetal malformations were detected during follow-up.

Congenital malformations in the IMID subgroup included pyelic ectasia (n = 3), patent foramen ovale (n = 2), patent ductus arteriosus (n = 1), short long bones (n = 1), and 9p deletion syndrome (n = 1). In the subgroup of healthy pregnant women, three congenital malformations were diagnosed: patent foramen ovale (n = 1), congenital portosystemic shunt (n = 1), and KID (Keratitis-Ichthyosis-Deafness) syndrome (n = 1). Although the difference was not statistically significant, only one fetal malformation was found in the RMD group compared to six in the IBD group. Malformations were not associated with DMARD use (cDMARDs, bDMARDs, or their combination) or with any DMARD used individually preconceptionally or during gestation.

The percentage of small-for-gestational-age (SGA) newborns was higher in patients with IMIDs and was associated with greater prematurity (p = 0.018). However, it was not associated with DMARD use (cDMARD or bDMARD) in patients with IMIDs. Earlier withdrawal of biologic DMARDs (mean 24 weeks) compared to later withdrawal (mean 30 weeks) was associated with a higher risk of preterm delivery (p = 0.024) and SGA (p = 0.050). No differences were found in APGAR scores at one and 5 min or fetal acidosis (measured by arterial pH in the umbilical cord) at birth.

4. Maternal-fetal outcomes and safety

Newborn infections were infrequent (4.35 %). Neonatal infections (n = 9) included bronchiolitis (n = 2), omphalitis (n = 2), herpangina (n = 2), meconium aspiration pneumonia, enterovirus infection, and acute pyelonephritis. No differences were observed between healthy and IMID pregnancies, between RMD and IBD, or with DMARDs (including steroids, cDMARDs, and bDMARDs).

5. Discussion

In general, patients with IMIDs who require treatment with bDMARDs have a more severe or refractory disease prior to gestation. However, in some patients, these bDMARDs (especially anti-TNF) are used preconceptionally to ensure good disease control in IMIDs previously controlled with teratogenic or potentially toxic cDMARDs during pregnancy or lactation.

5.1. Infection and flare

In our cohort, we observed a higher risk of flare among patients with

bDMARDs when these were discontinued early (before the eighth week). This higher risk in patients with bDMARDs may be due to the more severe and refractory nature of preconception IMID. Conversely, as previously noted in cohorts of RA patients, early withdrawal of bDMARDs is associated with an increased risk of flare [5,15].

While other studies have found that a higher risk of flare, as measured by CRP and clinical activity, is associated with a higher percentage of preterm deliveries [5], we were unable to demonstrate this relationship. However, in the subgroup of pregnancies under bDMARD, those who discontinued the drug earlier (mean 24 weeks) versus later (mean 30 weeks) had a higher risk of preterm birth and SGA.

In pregnant women with IBD, fecal calprotectin levels may be a useful marker for predicting future flares throughout gestation [16,17]. Other studies have evaluated the role of CRP, IL-6, and IL-21 in these patients [18]. However, we did not find relevant findings on CRP, nor did we routinely measure IL-6 or IL-21.

In pregnant women with RMD, biomarkers such as CRP, ESR, RF, and CCP were not useful in predicting which patients would experience a flare during or after gestation. Only HLA-B27 may play a role in predicting a flare in patients with AS. However, differentiating its predictive role from the intrinsic risk of AS to present a flare is complex. We did not identify other useful markers to predict which patients will experience disease activity.

A later last-dose-date of biologic was not associated with an increased risk of maternal or fetal infections. However, very early discontinuation of bDMARDs was associated with an increased risk of flare and steroid use. Steroid use had an elevated risk of maternal infections, specifically in the bDMARD subgroup.

5.2. Materno-fetal outcomes

Among maternal outcomes, we found that IMID patients require ART more often. This is likely due to advanced maternal age [19]. In our population, IMID women had an average age of 34 at the time of pregnancy, while healthy pregnant women had an average age of 31. Other factors, such as delayed maternity due to fear or potential harm of DMARDs, have not been evaluated but could contribute to the greater need for ART to achieve pregnancy in IMID women [20]. Despite maternal age, no differences were found in the risk of miscarriage or the calculated risk of aneuploidies between IMID and healthy pregnant women, with or without bDMARDs. The rate of miscarriage could not be studied, as most patients did not access pregnancy care until weeks 8–10 of gestation in the High-Risk Pregnancy Clinic.

Preeclampsia and labor induction rates were similar between IMID and healthy pregnancies. However, a higher risk of cesarean section was observed in patients on bDMARDs (Table 3). In IMID, the second leading cause of cesarean section after the loss of fetal well-being was induction failure, which was statistically significant. Although the cause is unclear, worse control of disease, increased digestive or pelvic joint activity, and higher failure rate of labor induction in patients on bDMARDs may have played a role.

Among fetal outcomes, there were no differences in congenital malformations between IMID and healthy patients. It is estimated that major fetal structural abnormalities occur in up to 3 % of all pregnancies [21]. Although there was only one fetal malformation in the RMD group and six in the IBD group, no association was found. Malformations were not correlated with DMARDs (cDMARDs, bDMARDs, or their combination) or any individual DMARDs used preconceptionally or during gestation.

A recent study by Auger et al. showed that the prevalence of congenital abnormalities was similar in pregnant women with and without IBD [22]. However, this study suggests that both types of IBD are associated with an increased risk of specific birth defects. Although the association with particular drugs was not assessed, the reduction of risk since 2000 suggests that the introduction of bDMARDs did not contribute to the pathogenesis of congenital abnormalities. Prospective studies should be conducted to confirm or update these risks and to develop clinical practice guidelines for managing IBD during pregnancy and breastfeeding. In this context, newer drugs like vedolizumab and Janus kinase inhibitors are of particular interest.

Although patients with IMIDs have a higher rate of SGA, there were no differences between patients with and without bDMARDs. However, in our population, earlier withdrawal of bDMARDs was associated with a higher risk of preterm delivery and SGA, which is consistent with other cohort studies [23]. Additionally, there were no differences in the APGAR test or neonatal acidosis at birth in patients receiving bDMARDs.

The limitations of this study include those inherent to a single-center cohort with IMIDs and controls. Despite the large sample size of the cohort, there is a possibility of selection bias. Furthermore, the prevalence of some diseases, treatments, and complications is low, which may limit the interpretation of the results. Future studies are needed to evaluate the correlation between congenital malformations and IMIDs, particularly in patients with IBD.

6. Conclusions

In conclusion, using bDMARDs in pregnant patients with IMIDs (RMD and IBD) appears to be effective in controlling disease activity while being safe for both mother and fetus, with no increase in prematurity, SGA, malformations, or infections. Our findings suggest that withdrawing bDMARDs during pregnancy may increase the risk of prematurity and SGA infants, underscoring the importance of maintaining these drugs throughout pregnancy in patients at high risk of disease flare. Furthermore, delaying the last dose of bDMARDs may allow for steroid-sparing, reducing the risk of flares and infections without increasing maternal-fetal complications. These results have important clinical implications and warrant further investigation in larger prospective studies.

Statement of ethics and consent

This study complied with the Declaration of Helsinki and was approved by the Local Ethics Commission. All the authors have read the instructions to the authors, and all accept the conditions posed.

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Declaration of competing interest

The author(s) declared no potential conflicts of interest concerning the research, authorship, or publication of this article.

Data availability

The data that has been used is confidential.

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