# Biologic therapy use and pregnancy outcomes in women with immune-mediated inflammatory rheumatic diseases

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## ABSTRACT

**Introduction:** Concerns about the side effects and interactions of biologic drugs with reproduction and pregnancy have been always an issue between experts. The safety of these therapies during conception and/or pregnancy is not fully understood. The aim of this study was to assess the exposure to biologic drugs before and/or during conception/pregnancy and the risk of adverse pregnancy outcomes in women with rheumatic diseases.

**Methods:** We conducted a cohort study of pregnancies reported in women with immune-mediated rheumatic diseases registered at the Rheumatic Diseases Portuguese Registry (Reuma.pt) and exposed to biologic drugs. Data concerning fetal and maternal outcomes (live birth, spontaneous abortion, neonatal and intrauterine death, intrauterine growth restriction, premature delivery, congenital malformations, neonatal lupus, voluntary or medical interruption of pregnancy, disease flares and need for treatment with other drugs) was extracted.

**Results:** In total, 69 pregnancies from 56 females were analyzed, the majority with the diagnosis of spondyloarthritis or rheumatoid arthritis. In almost half of the cases (n=32, 46.4%) the biologic was stopped for pregnancy planning, in 31 cases (44.9%) it was stopped when pregnancy was diagnosed and in 6 pregnancies (8.7%) biologic therapy was maintained, at least until the 2nd trimester. There were 76.8% of live births and 22% of spontaneous abortions. Congenital anomalies were reported in 2 newborns.

**Conclusions:** In half of the cases, it was decided to stop biologic therapy in the family planning period. Using biologic therapy before and/or during pregnancy doesn't seem to affect the overall maternal and fetal outcomes. Pregnancy planning and treatment options should be discussed and a shared decision should be established between physician and patient.

**Keywords:** Autoimmune diseases; Biologic therapy; Pregnancy.

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## INTRODUCTION

The increase use of biologic drugs in immune-mediated inflammatory rheumatic diseases arise concerns about their side effects and interactions with reproduction and pregnancy. There is no conclusive evidence on fetal safety of biologic therapy and its use before and during pregnancy, especially during the third trimester. However, evaluating the influence of these therapies in pregnancy is challenging because pregnant women are usually excluded from clinical trials. The use of biologic therapy in pregnancy, namely anti-tumor necrosis factor (anti-TNF) drugs, has been studied more extensively in inflammatory bowel diseases (IBD) than in rheumatic conditions[1].

Although the available results have been promising and do not seem to support a large excess risk of adverse pregnancy and fetal outcomes (embryo toxicity, teratogenicity or increased pregnancy loss), it is still difficult to state a solid conclusion[2–6]. In a 130 pregnancies cohort from Britain, 88 live births were reported in pa-

tients who received anti-TNF before or during pregnancy[3]. Another study of 417 pregnancies in rheumatoid arthritis (RA) where patients were exposed to anti-TNF drugs registered 387 normal deliveries.[4] There were no reports of maternal or fetal adverse outcomes in four patients treated with adalimumab in a study of 61 pregnant women with inflammatory arthropathies[7]. A recent analysis of 1137 pregnancies exposed to certolizumab does not suggest a teratogenic effect neither an increased risk of fetal death, compared to the general population[6].

There is not much data on the biologic treatment in female rheumatic patients who got pregnant, and on the respective medical approaches in Portugal. The aim of this study was to assess the exposure to biologic drugs before and/or during conception/pregnancy and the risk of adverse pregnancy outcomes in women with rheumatic diseases treated with biologic drugs.

## MATERIAL AND METHODS

### STUDY DESIGN AND POPULATION

We conducted a cohort study of pregnancies in women with immune-mediated inflammatory rheumatic diseases registered at the Rheumatic Diseases Portuguese Registry (Reuma.pt) who were exposed to biologic drugs. All women exposed to a bDMARD before pregnancy were included, regardless of having stopped treatment at the family planning period or maintaining the biologic drugs at the time of conception or throughout pregnancy.

### DATA COLLECTION

Demographic and clinical information was retrieved from Reuma.pt and completed during clinical appointment or by phone interviews, when needed. Collected data included demographic characteristics (age, race, height and weight), rheumatic disease diagnosis and disease duration (in years), comorbidities (arterial hypertension, dyslipidaemia, smoking and alcoholic consumption), current therapy [conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and bDMARDs] before, during and after pregnancy diagnosis), disease flares and need for treatment with other drugs during flares [csDMARDs, corticosteroids, nonsteroidal anti-inflammatory drug (NSAIDs)]. Obstetric history was also collected, including pregnancy follow-up (primary care physician, obstetrician, high risk outpatient clinic), type of delivery, birth weight, gestational complications and adverse birth outcomes.

### DEFINITIONS

A successful pregnancy was defined as a full-term live birth (≥ 37 weeks) with no malformations and no complications. Gestational complications and adverse birth outcomes were identified and registered by a gynaecologist/obstetrician and the ones included were:

- Pre-eclampsia: onset of high blood pressure during pregnancy;
- Spontaneous abortion: loss of a pregnancy without outside intervention before 20 weeks' gestation[8];
- Neonatal death (infant death <28 days of life) and intrauterine death (death at or after 28 weeks' gestation and before the complete expulsion or extraction from the mother)[9];
- Intrauterine growth restriction (IUGR) was considered when there was a poor growth of the fetus;
- Premature delivery was considered any birth before 37 completed weeks of gestation;
- Congenital malformations were considered when a birth defect, congenital disorders or congenital malformations were present[10];
- Neonatal lupus.

### STATISTICAL ANALYSIS

A descriptive analysis was performed using SPSS version 21.0 and data was summarized using means, standard deviations and percentages as appropriate.

This project was approved by the Ethics Committee of Centro Hospitalar e Universitário de Coimbra (Reference CHUC-097-17) and an informed consent was obtained from all patients.

## RESULTS

We included 56 woman with a mean age of 37.3±6.3 years, corresponding to a total of 69 pregnancies. The most frequent rheumatic disease diagnosis was spondyloarthritis (SpA) (42.9%) followed by RA (41.1%).The majority were non-smokers and had no drinking habits. Demographic data of the 56 women are resumed in Table I.

The biologic drug was stopped for pregnancy planning in 32 (46.4%) or when pregnancy was diagnosed in 31 (44.9%) of the 69 pregnancies. In the remaining 6 (8.7%) the biologic drug was maintained throughout pregnancy. From the 32 cases who stopped the

**TABLE I. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE 56 PATIENTS INCLUDED**

| Parameter | n (%) |
|---|---|
| Current age (years) (mean±SD) | 37.3±6.3 |
| Caucasian | 54 (96.4) |
| BMI (>25 kg/m2) | 32 (57.4) |
| Disease duration (years) (mean±SD) | 13.2±6.0 |
| Diagnosis | |
| Spondyloarthritis | 24 (42.9) |
| Rheumatoid arthritis | 23 (41.1) |
| Juvenile idiopathic arthritis | 4 (7.1) |
| Vasculitis | 4 (7.1) |
| Adult Onset Still's disease | 1 (1.8) |
| Smoking habits | |
| Current smoker | 8 (14.3) |
| Ex-smoker | 18 (32.1) |
| Never smoker | 30 (53.6) |
| Drinking habits (occasional) | 23 (41.1) |
| Comorbidities | |
| Arterial hypertension | 5 (8.9) |
| Hyperuricemia | 1 (1.8) |

BMI-Body Mass Index; SD-standard deviation

**TABLE II. MEDICATION BEFORE AND/OR DURING PREGNANCY**

| Parameter | n (%) |
|---|---|
| bDMARDs during pregnancy | |
| Etanercept | 1 (16.7) |
| Adalimumab | 1 (16.7) |
| Golimumab | 2 (33.3) |
| Tocilizumab | 1 (16.7) |
| Certolizumab | 1 (16.7) |
| Stoped biological treatment | |
| At pregnancy diagnosis | 31 (44.9) |
| Before conception | 32 (46.4) |
| Without interruption | 6 (8.7) |
| csDMARDs during pregnancy (3 missing data) | 22 (31.9) |
| Sulfassalazine | 13 (59.1) |
| Hydroxychloroquine | 5 (22.7) |
| Leflunomide | 1 (4.5) |
| Glucocorticoids during pregnancy (4 missing doses) | 30 (43.5) |
| Start/increase dose | 13 (43.3) |
| Decreased dose | 4 (13.3) |
| Maintained dose | 9 (30) |
| NSAIDs during pregnancy | 16 (23.3) |

bDMARDs- biological disease-modifying antirheumatic drugs; csDMARDs- conventional synthetic disease-modifying antirheumatic drugs; NSAIDs- nonsteroidal anti-inflammatory drugs

bDMARD for pregnancy planning, 12 (37.5%) were under adalimumab (ADA), 10 (31.3%) were treated with etanercept (ETN), 4 (12.5%) with golimumab (GOL), 3 (9.4%) with rituximab (RTX), 2 (6.3%) with infliximab (IFX) and 1 (3.2%) with tocilizumab (TCZ). From the 31 that stopped when pregnancy was diagnosed, 13 (41.9%) were treated with ETN, 10 (32.3%) with ADA, 5 (16.1%) with TCZ, 1 (3.2%) with IFX, 1 (3.2%) with GOL and 1 (3.2%) with anakinra. In 6 cases, the biologic treatment was maintained throughout pregnancy at least until the second trimester: 1 patient with ADA until 7$^{th}$ month, 1 with GOL until 6$^{th}$ month and 4 patients until delivery [ETN, GOL, TCZ and certolizumab (CZP)]. Twenty-two cases (31.9%) received concomitant csDMARDs during pregnancy, mostly sulfasalazine (Table II).

Of the 69 pregnancies, 53 (76.8%) newborns were delivered. Thirty nine (57.4%) pregnancies ended successfully, 10 resulted in preterm births, 15 in spontaneous abortions and 1 in an elective abortion. The majority of newborns were healthy with a weight ≥ 2500g, at full term and by vaginal delivery (Table III). There were 3 cases of IUGR: 1 case where ADA was maintained until 17 weeks of pregnancy which corresponded to the moment of pregnancy diagnosis; 1 case where ETN was stopped at the time the patient decided to become pregnant and 1 case where biologic treatment (TCZ) was continued throughout the pregnancy. Two congenital malformations were identified: 1 newborn with hypospadias (mother under ADA until family planning period) and 1 newborn with cleft palate (mother with ADA until 17 weeks pregnancy). Of the 15 spontaneous abortions, 2 had positive thrombophilia study and 1 was an ectopic pregnancy; the remaining cases had no other common causes identified. There were no registered cases of neonatal death.

Regarding the 6 pregnancies under biologic treatment: three cases were full term births without any complication (ETN=1; CZP=1; ADA=1) and one case treated with GOL was a preterm birth; in one case (a woman with vasculitis and a 38 weeks pregnancy under TCZ), an IUGR was detected; one patient treated with GOL and leflunomide was submitted to an elec-

**TABLE III. OUTCOMES OF THE 69 PREGNANCIES**

| Parameter | n (%) |
|---|---|
| Live births | 53 (76.8) |
| Gestational age at delivery (weeks) (1 without information) | |
| ≥37 | 42 (80.8) |
| <37 | 10 (19.2) |
| Spontaneous abortion | 15 (21.7) |
| Elective abortion | 1 (1.4) |
| Type of delivery of live births (2 without information) | |
| Vaginal | 30 (58.8) |
| Instrumentalized vaginal birth | 7 (23.4) |
| Non instrumentalized vaginal birth | 23 (76.6) |
| Cesarean | 21 (41.2) |
| Weight of live newborn (g) (4 without information) | |
| ≥2500g | 38 (77.5) |
| <2500g | 11 (22.5) |
| Congenital malformations | 2 (2.9) |

bDMARDs- biological disease-modifying antirheumatic drugs; csDMARDs- conventional synthetic disease-modifying antirheumatic drugs; NSAIDs- nonsteroidal anti-inflammatory drugs

tive abortion at 8 weeks because of anembryonic pregnancy.

Disease flares occurred in 21.7% of patients (n=15) mostly during the 1st and 2nd trimesters: 6 patients stopped biologic treatment when pregnancy was diagnosed, 7 stopped for pregnancy planning and 2 patients maintained treatment throughout pregnancy. One case of pre-eclampsia was reported (a woman who stopped ETN at the 1st trimester). About 23% and 43% of patients respectively received NSAIDs and glucocorticoids during pregnancy for rheumatic disease control. Twenty-six pregnancies (37.7%) were followed in high risk outpatient clinic.

Comparing the successful and unsuccessful pregnancies, RA and SpA were the most frequent diagnosis in the first and second group, respectively (Table IV). There were more current smokers in the group with successful pregnancies. The majority of women with successful pregnancies stopped biologic drugs at family planning period. Two women in the group with successful pregnancies and 4 women in the unsuccessful pregnancy group maintained treatment until the end of pregnancy (ADA and CZP in the first group and ETN, GOL and TCZ in the second group). There was a greater need to use csDMARDs in the successful pregnancy group.

## DISCUSSION

The introduction of bDMARDs had a significant impact in the outcomes of rheumatic conditions[11]. However, their use during conception and/or pregnancy is still a matter of debate. In 2003, 175 rheumatologists and members of American College of Rheumatology answered a questionnaire about their perception of fetal risk associated to some DMARDs (methotrexate, leflunomide, ETN and IFX) and high agreement was observed regarding the risk of teratogenicity with methotrexate and leflunomide but there was no consensus about ETN or IFX[12].

Anti-TNF drugs are the most studied biologic drug class in pregnancy, especially in patients with IBD[1]. Most of the available safety data is based on women who discontinued anti-TNF therapy during the first trimester and, apparently, the exposure to these drugs at conception or during early pregnancy is not associated with adverse pregnancy outcomes or any increase in congenital abnormalities, when compared to unexposed females, as in our cohort[1,12-21]. Mahadevan *et al.* followed 10 women that received intentional IFX during pregnancy and all of them ended in live births without any adverse fetal outcomes[21]. In one study with 72 pregnancies exposed to IFX or ADA (last median gestational week of IFX and ADA administration was 29 and 30, respectively), 7 were preterm delivery[19]. In our cohort, there were 10 cases of preterm birth but only 3 had some exposition to a biologic drug (GOL, ETN, TCZ). In all cases from our cohort, the last bDMARD administration was before week 24. Hoxha *et al.* followed prospectively 38 pregnancies and 24 were exposed to anti-TNF at 1st trimester, 11 prior to conception and 3 following paternal exposure[14]. They reported 2 congenital malformations: 1 newborn that was exposed to ADA at 1st trimester and another whom mother suspended ETN for pregnancy planning[14]. We also identified 2 congenital malformations; both women were treated with ADA but 1 stopped treatment for pregnancy planning and the other remained until 2nd trimester.

On the other hand, the exposure in late pregnancy is associated with drug levels in the newborn and their long-term effects remain unknown[11]. The amount of drug that crosses the placenta varies depending on drug

**TABLE IV. CLINICAL CHARACTERISTICS OF SUCCESSFUL AND UNSUCCESSFUL PREGNANCIES**

| | Successful pregnancy (n=39) | Unsuccessful pregnancy (n=29) |
|---|---|---|
| Current age (years) (mean±SD) | 37.7 ±6.3 | 38.2 ±6.2 |
| Diagnosis | | |
| Spondyloarthritis n(%) | 16 (41) | 14 (48.3) |
| Rheumatoid arthritis n(%) | 18 (46.2) | 10 (34.5) |
| Juvenile idiopathic arthritis n(%) | 3 (7.7) | 2 (6.9) |
| Vasculitis n(%) | 1 (2.6) | 3 (10.3) |
| Adult Onset Still's disease n(%) | 1 (2.6) | |
| Comorbidities | | |
| Current smoker n(%) | 7 (17.9) | 2 (6.9) |
| Arterial hypertension n(%) | 4 (10.3) | 3 (10.3) |
| bDMARDs | | |
| STOPED before conception | 22 (56.4) | 10 (34.5) |
| STOPED at pregnancy diagnosis | 15 (38.5) | 15 (51.7) |
| Without interruption | 2 (5.1) (ADA, CZP) | 4 (13.8) (TCZ, ETN, GOL=2) |
| csDMARDs during pregnancy (2 without information) | 15 (38.5) | 6 (20.7) |
| Sulfassalazine | 8 (53.3) | 5 (83.3) |
| Hydroxychloroquine | 5 ( 33.3) | |
| Leflunomide | | 1 (16.7) |

Successful pregnancy was defined as a full term live birth with no malformations and no complications.
ADA-Adalimumab; bDMARDs- biological disease-modifying antirheumatic drugs; csDMARDs- conventional synthetic disease-modifying antirheumatic drugs; CZP-Certolizumab; ETN-Etanercept; GOL-Golimumab; TCZ-Tocilizumab;
SD-standard deviation

structure. Monoclonal antibodies (IFX, ADA and GOL) cross the placenta at the third trimester, while the amount is much less with ETN (fusion protein) and CZP (antibody fab fragment)[15]. Shannon L. Kanis *et al.* found that, in a group of women with IBD, anti-TNF concentrations in cord and maternal blood were higher in the IFX group than in the ADA group. However, one-year health outcomes of the exposed infants were similar between the 2 groups[22]. Dana Duricova *et al.* assessed the impact of in utero exposure to anti-TNF on women with IBD. In this study there were no significant differences between exposed children and controls regarding growth, psychomotor development or infectious complications within the first year. [23] In a cohort of women with RA treated with CZP or ETN, there was no association between bDMARD use and adverse pregnancy outcomes (abortion, preterm birth, light-for-date [birth weight lower than the 10th percentile] and premature rupture of the membranes). Interestingly, the birth weight of newborns was higher and the mean time to pregnancy was significantly shorter when compared to patients that discontinued bDMARDs and csDMARDs at the time of planning to conceive[24]. A recent trial showed that biologic therapy in pregnant IBD patients did not lead to any adverse fetal or maternal outcomes such as rates of low birth weight, caesarean section or neonatal intensive-care unit (NICU) stay. However, when adding therapy with azathioprine or 6- mercaptopurine the rates of pre-term birth, low birth weight and NICU where higher[25].

Overall, our cohort demonstrated successful maternal and fetal outcomes (low incidence of gestational complications and adverse birth outcomes defined previously) which are in agreement with the previous published literature. In half cases, the biologic was suspended before conception. Fifty seven percent of successful pregnancies were recorded, according to our strict definition. From the 6 pregnancies under biologic treatment, just one case of IUGR and another of anembryonic pregnancy were registered. However, in the last case, the mother was also under leflunomide that is known to be embryo toxic and teratogenic in ro-

dents[26] but less data in humans and we are not able to establish a direct causal relationship between the treatment used and the pregnancy outcome. Two cases (2.8%) of congenital malformations were identified (hypospadias and cleft palate), which is in line with the prevalence reported in the general population[27]. In both cases, women have been exposed to ADA. These 2 cases are insufficient to suggest any causality. Furthermore, in one of the cases, the mother has stopped ADA at least one year before conception.

The risk of infection is one of the major concerns for all biologics. Recently, in a 10-year study that included women using biologic drugs during pregnancy and infants exposed in utero, Nicole Tsao *et al.* reported an absence of increased infections risk requiring hospitalization in mothers during post-partum or in infants during the first year of life. Still, the infectious risk in these periods is already elevated due to delivery and post-partum period themselves and because of the naïve immune system of the new-born [28]. Unfortunately, we were not able to assess the risk of infection in newborns that were exposed to biologic drugs because we hadn't access to newborn's medical records. A French study showed an increased risk of maternal complications (specifically infections) but none for infants up to 1 year of life when exposed to anti-TNF drugs in utero. Also, stopping anti-TNF before week 24 was associated to an increased risk of disease flare, that could offer an escape and alternative to the current guidelines[29].

EULAR recommendations are favorable to the use of anti-TNF during the first trimester of pregnancy. In these recommendations, ETN or CZP can also be considered throughout pregnancy, if necessary, due to their low rate of transplacental passage. Other bDMARDs such as RTX, anakinra, TCZ, abatacept, belimumab and ustekinumab have limited information and should be stopped before conception[13]. During pregnancy, safe cDMARDs (hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, ciclosporin, tacrolimus and colchicine) could be used for a better disease control (if needed) but this should be an individual decision[13].

This study has some highlight aspects. First, as far as we know this is the first study in Portugal evaluating pregnancy outcomes in women under biologic drugs. Second, it is a multicenter study that allows us to have a global vision of Portuguese reality. The lack of clinical trials in this area reinforces the need for observational studies to complete and complement the knowledge of the health professional.

However, some limitations can be acknowledged. The small sample size and retrospective analysis could be an issue for selection and information bias. The limited number of pregnancies exposed to biologic drugs is limiting to draw robust conclusions. Newborns have follow-up in different hospitals from their mother and we didn't have access to medical records that would be important to assess other fetal outcomes, such as the risk of infections. Incomplete medical records and the possibility for the existence of cases not registered at Reuma.pt represent additional limitations.

## CONCLUSION

The choice of biologic therapy should be individualized and based on its ability to control disease activity as well as its safety profile for the fetus. From the obtained data, it appears that previous or current exposure to biologic treatments is compatible with a successful pregnancy. A timely and careful planning is the key to success and should include a risk-benefit weighting the use of this type of treatment during this period. Although there is no clear medical evidence from randomized controlled trials, observational studies are important in order to give us some information about fetal prognosis and safety but truly and definitive conclusions remain mainly speculative. There is a need for more clinical studies regarding this subject, namely information about the safety of the new biologics.

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