

# Baricitinib exposure during pregnancy in rheumatoid arthritis

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## Abstract

We here describe the case of a 43-year-old White woman who was diagnosed with rheumatoid arthritis treated with anti-tumour necrosis factor drugs that caused an adverse drug reaction. The objective of this study was to describe the outcome of a pregnancy under baricitinib, a JAK-inhibitor drug, in a woman affected by rheumatoid arthritis. Scant data are available about the safety of JAK inhibitors during pregnancy. A case report and review of literature about JAK-inhibitor exposure during pregnancy were conducted. After the failure of biologic disease-modifying antirheumatic drugs due to a loss of efficacy and adverse drug reaction, the patient was started on baricitinib when it was marketed. During the fifth month of this treatment, she reported missing her period and a pregnancy was confirmed, despite a previous recommendation of adequate contraception. Thus, she had been exposed to baricitinib for several weeks before conception and during the whole first-trimester until the 17th week of gestation. The treatment with baricitinib was promptly discontinued and she was regularly examined. Foetal growth was normal throughout pregnancy and ultrasound examination did not detect any macroscopic abnormality. This is the first report of exposure to baricitinib during pregnancy outside the drug registration study program. We report the positive pregnancy outcome of a continuous exposure to baricitinib during the first 17 weeks of pregnancy. Small molecules, such as JAK inhibitors, are increasingly being used in clinical practice in rheumatoid arthritis and in other diseases. Hence, more broad and focused studies are required to have an insight of safety for this drug class in the case of accidental exposure before or during pregnancy.

**Keywords:** adverse drug reaction, JAK inhibitors, pregnancy, rheumatoid arthritis, synthetic DMARDs

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We report a case of a 43-year-old woman affected by rheumatoid arthritis (RA) who became pregnant under baricitinib treatment. Her clinical history begun when she was 25 years old with arthritis of the hands, wrists, and knees. On examination, there was swelling and tenderness of wrists and of all metacarpophalangeal joints and proximal interphalangeal joints. The inflammatory markers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were respectively 17.5 mg/dl and 45 mm/h and her DAS28-CRP score at the onset was 5.26. She was positive for IgM rheumatoid factor and anticyclic citrullinated peptides antibodies

at high titre. She had no active or past extra-articular clinical involvement. She also had two previous pregnancies at term without complications.

The patient had been treated with methotrexate as monotherapy up to 20 mg/week, then associated with etanercept 50 mg/week subcutaneously achieving remission, but this line of treatment failed after 2 years. Then, she had been switched to adalimumab and she achieved low disease activity. Unfortunately, during adalimumab treatment she reported systemic reaction (urticaria and angioedema) and also local erythema and

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hives at the site of injection. We performed a skin-prick test according to available protocols, which was positive for adalimumab. We chose certolizumab as a third-line treatment with anti-tumour necrosis factor (TNF), but the patient had adverse drug reactions from the first injection. To evaluate the adverse drug reaction, we performed skin drug testing using certolizumab pegol, which resulted in cutaneous and systemic drug reaction, as she suffered respiratory symptoms and hypotension associated with local pruritus and injection-site reaction.

After that, she refused other treatments with conventional and biologic disease-modifying antirheumatic drugs (DMARDs) and she was treated only with oral corticosteroids (prednisone dose: 10 mg/day) and NSAID courses as needed for 3 years. Afterward, due to persistent disease activity, she was started on baricitinib when it was marketed.<sup>1</sup> At first follow up, after 3 months, the disease was in remission (DAS28-CRP of 1.96) with normalization of inflammatory markers (CRP of 1.5 mg/dl; ESR of 10 mm/h). She did not have any tender or swollen joints and also, she did not complain of joint pain.

Before starting the therapy with baricitinib at 4 mg/day, we requested a pregnancy test, which was negative. During the fifth month of therapy, the patient reported missing her period and her pregnancy was confirmed, despite previous recommendations of adequate contraception. Thus, we can estimate an exposure to baricitinib for a few weeks before conception and during the whole first trimester until the 17th week of gestation. The treatment with baricitinib was promptly discontinued and she was regularly examined. Symptoms were then controlled by corticosteroid treatment (methylprednisolone at doses between 8 and 16 mg/day). Foetal growth was normal throughout the pregnancy and ultrasound examination did not detect any macroscopic abnormality.

The infant was born at term at 38 weeks after a repeat Caesarean section, because in the past pregnancies she underwent Caesarean section for cephalopelvic disproportion and because of the mother's age. There were no complications for the mother and the newborn, who had normal weight (3,200 g) and length (50 cm) at birth and early development. No perinatal infections occurred. The mother decided to continue only corticosteroid therapy during breastfeeding with methylprednisolone at 8 mg/day, together with

infiltration of steroids into the metacarpal joints, with partial efficacy. She refused to restart therapy with baricitinib or other drugs while she was continuing to breastfeed the baby. At 9 months of age, the baby had normal growth and psychomotor development, with no clinical nor laboratory alterations. Afterwards the infant started to receive vaccinations according to the national Italian schedule without significant adverse events.

As stated by the European League Against Rheumatism, the points to consider<sup>2</sup> are that most of the antirheumatic drugs can be used safely throughout pregnancy and lactation. The fact that the use of a drug is not recommended during pregnancy or lactation does not necessarily mean that there is a proven evidence of risk for the child. It generally reflects the current paucity of data; therefore, a cautionary approach is preferred. Meanwhile more information will be available regarding the safety of the use of the drug. Conversely, only a few drugs, such as methotrexate, mycophenolate and cyclophosphamide are known teratogens and should be stopped before conception in order to allow an adequate washout period. Scant data are available for targeted synthetic DMARDs inhibiting JAK.

In addition to the crucial role in the signalling of immune cell development, the JAK-STAT pathway has been shown to be involved in cell-cell adhesion and in cell polarity, which could condition the earlier stages of embryonic development.<sup>3</sup> In murine models, baricitinib, at doses higher than 20-times the human labelled dose, has shown to reduce fertility, to have a teratogenic effect, reduce bone growth and foetal weight in the uterus, and increase embryolethality.<sup>3</sup>

There are not enough data regarding baricitinib exposure during breastfeeding, nor whether it can be transferred in the human milk.<sup>4</sup>

The current recommendation is that the use of baricitinib should be stopped at least 1 month before conception.<sup>3</sup> No data are available on the transfer of baricitinib into human breastmilk nor on the health conditions of newborns who were breastfed during maternal treatment with baricitinib. Therefore, a decision must be made whether to discontinue breastfeeding or to discontinue treatment, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.<sup>3</sup>

The exposure to tofacitinib, a different oral JAK inhibitor, during conception and pregnancy in rheumatic diseases or ulcerative colitis seems not to be associated with increased risk to the foetus when compared with risks linked to the underlying disease.<sup>2,5,6</sup> As for other drugs used in RA, to date there are no data showing teratogenicity of JAK inhibitors.

This case is the first report of exposure to baricitinib during pregnancy outside the drug registration study program; in this case it shows a positive outcome of a continuous exposure to baricitinib during the first 17 weeks of pregnancy without evidence of teratogenic effects.

In the past decade, biological agents have proved to be very effective treatments for RA patients in certain circumstances, as well as during pregnancy for maintenance of remission or treatment of a disease flare.<sup>1,2</sup> However, drug hypersensitivity, treatment failure or paradoxical effects of this widely used drug class are not infrequently observed in clinical practice: thus, the exposure to other drug classes, including small molecules as JAK inhibitors, is steadily increasing. Our experience may be useful when counselling those women who inadvertently get pregnant during baricitinib use. Hence, more broad and focused studies are required in order to have an insight of safety for this class of drugs during pregnancy and lactation.

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### Conflict of interest statement

The authors declare that there is no conflict of interest.

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