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ORIGINAL RESEARCH ARTICLE

Pregnancy Outcomes in Patients Treated with Upadacitinib: Analysis of Data from Clinical Trials and Postmarketing Reports

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Abstract

Background and Objective Upadacitinib is indicated for diseases affecting persons of childbearing potential including rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, atopic dermatitis, Crohn's disease, and ulcerative colitis; however, teratogenicity was observed in animal studies. Given the potential for human fetal risk, pregnancy avoidance measures were required during clinical trials. This analysis describes pregnancy outcomes in patients exposed to upadacitinib during pregnancy.

Methods Clinical trial and postmarketing cases of in utero exposure to upadacitinib were identified in AbbVie's safety database through 25 April, 2023. Analysis of clinical trial cases and postmarketing reports are presented separately; prospective and retrospectively reported pregnancy outcomes are integrated for each. Descriptive rates are presented to summarize outcomes.

Results There were 128 maternal upadacitinib-exposed pregnancies with known outcomes identified; 80 and 48 pregnancies were reported in clinical trials and the postmarketing setting, respectively. In clinical trials (mean in utero exposure of 5 weeks, 3 days), live births (54%), spontaneous abortions (24%), elective terminations (21%), and ectopic pregnancy (1%) were reported. There was one report of a congenital malformation: a 35-week infant with an atrial septal defect. In postmarketing cases, live births (46%), spontaneous abortions (38%), elective terminations (15%), and ectopic pregnancy (2%) were reported.

Conclusions As the data are limited for in utero exposure to upadacitinib, definitive conclusions cannot be drawn regarding the effect of upadacitinib on pregnancy outcomes. Rates of adverse pregnancy outcomes with upadacitinib exposure were comparable to rates observed in the general population or patients with autoimmune inflammatory diseases. To date, no apparent evidence of teratogenicity exists in the analyses of human pregnancies exposed to upadacitinib during the first trimester.

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Key Points

Persons of childbearing potential may have chronic inflammatory diseases for which upadacitinib treatment could be prescribed; however, pregnancy avoidance measures should be taken given the product label warns of the potential for a fetal risk with in utero exposure.

In the clinical trial data available from exposure to upadacitinib during the first trimester, rates of adverse pregnancy outcomes do not appear higher than what may be observed in the general population or in patients with autoimmune inflammatory disease not receiving upadacitinib.

Given there are limited data available for pregnancy outcomes from upadacitinib-exposed pregnancies during clinical trials and the postmarketing setting, definitive conclusions cannot be drawn regarding the effect of upadacitinib on pregnancy outcomes.

1 Introduction

Persons of childbearing potential can be burdened with rheumatologic, dermatologic, and inflammatory bowel diseases requiring systemic treatment. Upadacitinib, an oral Janus kinase (JAK) inhibitor engineered for increased selectivity for JAK1, is approved for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, nonradiographic axial spondyloarthritis, atopic dermatitis, ulcerative colitis, and Crohn's disease [1]. Upadacitinib has been assessed in phase II and III studies at doses of 3 mg, 6 mg, 12 mg, or 24 mg twice daily, and/or 7.5 mg, 15 mg, 30 mg, 24 mg, or 45 mg once daily, depending on the study indication and formulation, and has a mean terminal elimination half-life of 8–14 h [1–4]. Data on pregnancy outcomes are limited because pregnancy avoidance measures are required during upadacitinib administration in clinical trials and in the marketed setting. Data accrued in clinical trials are mostly limited to first-trimester exposure given patients are required to discontinue treatment immediately if they become pregnant. Limited data exist in the literature regarding the use of other JAK inhibitors (e.g., tofacitinib, baricitinib, abrocitinib) during pregnancy.

In animal embryofetal development studies, oral upadacitinib administration to pregnant rats and rabbits at exposures equal to or greater than approximately 1.6 and 15 times the 15-mg dose, 0.8 and 7.6 times the 30-mg dose, and 0.6 and 5.6 times the maximum recommended human dose of 45 mg (on an area under the curve basis) resulted in dose-related increases in skeletal malformations (rats only), an increased incidence of cardiovascular malformations (rabbits only), increased post-implantation loss (rabbits), and decreased fetal body weights (in both rats and rabbits) [1]. Because of these preclinical findings, clinical trials with upadacitinib required patients of childbearing potential to use at least one method of highly effective contraception during the study and for 4 weeks after the last dose of study drug to avoid pregnancy. Patients of childbearing potential were required to take a pregnancy test prior to the study start and monthly (testing done at home when in between visits) during the upadacitinib clinical trials. Pregnant patients or those planning to become pregnant were not allowed to enroll, and patients who became pregnant were immediately discontinued from the study drug. Because patients of childbearing potential had to undergo pregnancy testing on a monthly basis throughout a clinical trial, the majority of pregnancies that occurred in clinical studies were detected early in gestation, most often during the first trimester of pregnancy.

When pregnancies did occur, patients were followed and outcomes were collected, when possible. In some upadacitinib studies, patients were allowed to be on background methotrexate, a medication associated with teratogenicity and fetotoxicity in human pregnancy [5]. Here, we report the first analysis of cumulative pregnancy outcomes with known maternal upadacitinib-exposure using data collected from clinical trials and postmarketing cases from the AbbVie global safety database.

2 Materials and Methods

2.1 Data Source and Methods

An AbbVie global safety database search, which includes regulatory mandated safety data from AbbVie-sponsored clinical trials and unsolicited postmarketing reports received by AbbVie, was conducted to identify all reports of pregnancy through 25 April, 2023 using an AbbVie Customized MedDRA Query Medical Dictionary for Regulatory Activities. A full list of preferred terms assessed is included in Table S1 of the Electronic Supplementary Material (ESM). Clinical studies included in this analysis are composed of the following approved indications: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, nonradiographic axial spondyloarthritis, atopic dermatitis, ulcerative colitis, and Crohn's disease. In some studies (excluding atopic dermatitis), concomitant methotrexate was allowed. Clinical trial cases are analyzed separately from postmarketing reports; however, within each group, prospective and retrospective reports of pregnancy were integrated and analyzed. A prospective report is when pregnancy data are acquired prior to the knowledge of the pregnancy outcome or prior to the detection of a congenital

malformation at a prenatal exam (i.e., via fetal ultrasound). A retrospective report is pregnancy data acquired after the outcome of the pregnancy is known or after the detection of a congenital malformation on a prenatal test. Ideally, only prospective, medically confirmed reports of pregnancy would be presented as they are reported before known outcomes and without reporting bias. Retrospective reports often have limitations because of patient memory recall and reporting bias (adverse outcomes are reported more than normal outcomes). However, based on the limited number of reports with a known outcome in this comprehensive analysis, prospective and retrospective reports of pregnancy are combined to describe the totality of the data.

Maternal upadacitinib-exposed pregnancies and pregnancy outcomes, including live births with or without congenital anomalies, spontaneous abortions, elective terminations, ectopic pregnancies, and those lost to follow-up or ongoing are described separately for pregnancy reports from the upadacitinib clinical program and postmarketing surveillance. For clinical trials, demographic and clinical characteristics, as well as disease activity at the time of pregnancy (defined as the last observation on or before the patient's last menstrual period), for each indication and overall are also described. The gestational exposure timing in weeks and days was calculated using the date of the last recorded menstrual period and the end date of upadacitinib treatment; mean and median values were comparable, and means are reported here. Given there is no meaningful systemic exposure to a fetus via seminal transmission of upadacitinib and therefore no expected risk to the fetus [6], paternal exposure reports of pregnancies in partners of male study patients were not proactively collected throughout all clinical studies and thus will not be presented in this analysis.

2.2 Ethical Statement

Each individual trial included in this report was conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and was consistent with International Conference on Harmonization Good Clinical Practice, Good Epidemiology Practices, and applicable regulatory requirements. All patients provided written informed consent before enrolling in each clinical trial. Each individual trial included in this report was approved by an independent ethics committee/institutional review board at each study site (Table S2 of the ESM). Initial submission of unsolicited postmarketing reports by physicians or patients is voluntary. For the collection of further information after the initial report, a reporter's consent was obtained through a query in the global safety database. Authors had access to de-identified anonymized data to prepare this report.

3 Results

3.1 Clinical Trial Pregnancy Cases and Outcomes

3.1.1 Patient Demographics and Clinical Characteristics

At the time of the data cutoff, 5234 persons of childbearing potential (defined as female individuals aged 15–55 years) had received at least one dose of upadacitinib in a clinical study. A total of 97 maternal exposure pregnancies among 96 patients (one patient experienced two distinct pregnancies) with in utero exposure to upadacitinib were identified in the upadacitinib clinical trials across indications; of these 97 pregnancies, 17 were ongoing or lost to follow-up at the time of the data cutoff, leaving 80 pregnancies with known outcomes. Table 1 summarizes demographic and clinical characteristics at the start of the reported pregnancy ($n = 80$), stratified by disease indication. A table summarizing this information for all pregnancies, including those lost to follow-up or ongoing, is available in Table S3 of the ESM.

The age range of patients who became pregnant was 27–33 years, with a mean (standard deviation) age of 31.1 $\pm$ 6.2 years. At the time of pregnancy, more than half (63.8%) of patients had received their disease diagnosis $\geq$ 5 years prior. In total, 26.3% ($n = 21/80$) of patients were receiving concomitant methotrexate at the start of pregnancy, with a mean (standard deviation) dose of 16.4 $\pm$ 4.5 mg/week; all of these patients were enrolled in rheumatoid arthritis or psoriatic arthritis studies. About a quarter ($n = 23$, 28.8%) of patients were receiving concomitant oral corticosteroids (rheumatoid arthritis: $n = 22$; ulcerative colitis: $n = 1$), with a mean prednisone equivalent daily dose of 6.0 $\pm$ 3.7 mg.

Disease activity status varied by disease indication. More than half of patients with rheumatoid arthritis and psoriatic arthritis were in remission or had minimal disease activity at the start of pregnancy. Nearly all patients with non-radiographic axial spondyloarthritis (100%), atopic dermatitis (95.7%), and Crohn's disease (100%) had achieved an inactive disease state or a state of disease control at the start of pregnancy. Only 40% of patients with ulcerative colitis were in clinical remission based on the Adapted Mayo Score.

3.1.2 Pregnancy Reports and Outcomes

Of the 80 pregnancies with known outcomes, prospective ($n = 69$) and retrospective ($n = 11$) cases were combined because of limited numbers, with the majority being prospective, based on the nature of close monitoring for

Table 1 Demographic and clinical characteristics at the start of pregnancies with known outcomes ($n = 80$) observed in clinical trials

	Rheumatoid arthritis ($n = 34$)	Psoriatic arthritis ($n = 6$)	nr-axial spondyloarthritis ($n = 1$)	Atopic dermatitis ($n = 23$)	Ulcerative colitis ($n = 10$)	Crohn's disease ($n = 6$)	Total ($N = 80$)
Patient characteristics							
Age [years], mean $\pm$ SD	33.2 ± 5.7	33.3 ± 4.6	$27.0 \pm$ N/A	27.7 ± 7.4	31.4 ± 4.6	30.2 ± 2.7	31.1 ± 6.2
Age group [years], n (%)							
< 20	0	0	0	4 (17.4)	0	0	4 (5.0)
20–24	1 (2.9)	0	0	5 (21.7)	0	0	6 (7.5)
25–29	10 (29.4)	2 (33.3)	1 (100)	5 (21.7)	5 (50.0)	2 (33.3)	25 (31.3)
30–34	9 (26.5)	2 (33.3)	0	4 (17.4)	3 (30.0)	4 (66.7)	22 (27.5)
35–39	10 (29.4)	1 (16.7)	0	2 (8.7)	1 (10.0)	0	14 (17.5)
40–44	4 (11.8)	1 (16.7)	0	3 (13.0)	1 (10.0)	0	9 (11.3)
$\geq$ 45	0	0	0	0	0	0	0
BMI [kg/m^2], mean $\pm$ SD	28.7 ± 7.1	25.8 ± 4.9	$18.4 \pm$ N/A	25.7 ± 5.6	24.2 ± 3.7	25.7 ± 4.4	26.7 ± 6.2
BMI category [kg/m^2], n (%)							
< 30	22 (64.7)	4 (66.7)	1 (100)	18 (78.3)	7 (70.0)	5 (83.3)	57 (71.3)
$\geq$ 30	12 (35.3)	2 (33.3)	0	4 (17.4)	2 (20.0)	1 (16.7)	21 (26.3)
Unknown	0	0	0	1 (4.3)	1 (10.0)	0	2 (2.5)
Time since diagnosis [years]							
Mean $\pm$ SD	6.6 ± 5.3	7.0 ± 3.4	$5.1 \pm$ N/A	20.0 ± 10.1	7.5 ± 4.1	6.8 ± 3.7	10.6 ± 9.0
< 5 years, n (%)	18 (52.9)	3 (50.0)	0	3 (13.0)	3 (30.0)	2 (33.3)	29 (36.3)
$\geq$ 5 years, n (%)	16 (47.1)	3 (50.0)	1 (100)	20 (87.0)	7 (70.0)	4 (66.7)	51 (63.8)
Treatment history							
Concomitant corticosteroids (all routes), n (%)	22 (64.7)	0 (0.0)	0 (0.0)	7 (30.4)	1 (10.0)	0 (0.0)	30 (37.5)
Concomitant corticosteroid prednisone equivalent dose [mg] (all routes), mean $\pm$ SD	5.4 ± 2.1	–	–	0.5 ± 0.5	$20.0 \pm$ N/A	–	4.7 ± 4.0
Concomitant topical glucocorticoids, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	7 (30.4)	0 (0.0)	0 (0.0)	7 (8.8)
Concomitant topical glucocorticoids dose [mg], mean $\pm$ SD	–	–	–	0.5 ± 0.5	–	–	0.5 ± 0.5
Concomitant oral glucocorticoids, n (%)	22 (64.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	23 (28.8)
Concomitant oral glucocorticoids dose [mg], mean $\pm$ SD	5.4 ± 2.1	–	–	–	20.0 ± 0.0	–	6.0 ± 3.7
Concomitant MTX, n (%)	19 (55.9)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	21 (26.3)
Concomitant MTX dose [mg/week], mean $\pm$ SD	16.6 ± 4.4	15.0 ± 7.1	–	–	–	–	16.4 ± 4.5
Concomitant NSAIDs, n (%)	18 (52.9)	0 (0.0)	0 (0.0)	2 (8.7)	1 (10.0)	0 (0.0)	21 (26.3)
Concomitant narcotic analgesics, n (%)	2 (5.9)	0 (0.0)	0 (0.0)	1 (4.3)	1 (10.0)	0	4 (5.0)
Disease activity, n (%)							
Clinical Disease Activity Index remission ($\leq$ 2.8)	19 (55.9)	–	–	–	–	–	–
DAS28 (CRP) remission (< 2.6)	22 (64.7)	–	–	–	–	–	–
DAPSA remission ($\leq$ 4)	–	3 (50.0)	–	–	–	–	–
MDA[a]	–	4 (66.7)	–	–	–	–	–
Achievement of EASI 75	–	–	–	22 (95.7)	–	–	–
vIGA-AD 0/1 achievement	–	–	–	21 (91.3)	–	–	–
ASDAS LDA (< 2.1)	–	–	1 (100)	–	–	–	–
ASDAS ID (< 1.3)	–	–	1 (100)	–	–	–	–

Table 1 (continued)

	Rheumatoid arthritis ($n = 34$)	Psoriatic arthritis ($n = 6$)	nr-axial spondyloarthritis ($n = 1$)	Atopic dermatitis ($n = 23$)	Ulcerative colitis ($n = 10$)	Crohn's disease ($n = 6$)	Total ($N = 80$)
Clinical remission per adapted Mayo score[b]	–	–	–	–	4 (40.0)	–	–
Clinical remission per CD Activity Index (<150)	–	–	–	–	–	6 (100)	–

Baseline is defined as the last non-missing observation on or before the patient's reported last menstrual period. One patient had two pregnancies that are counted separately in this table

ASDAS Ankylosing Spondylitis Disease Activity Score, *BMI* body mass index, *CD* Crohn's Disease, *CRP* C-reactive protein, *DAPSA* Disease Activity Index for Psoriatic Arthritis, *DAS28* Disease Activity Score 28, *EASI 75* 75% reduction from baseline in the Eczema Area and Severity Index, *ID* inactive disease, *LDA* low disease activity, *MDA* minimal disease activity, *MTX* methotrexate, *nr* nonradiographic, *NSAIDs* non-steroidal anti-inflammatory drugs, *SD* standard deviation, *vIGA-AD* Validated Investigator Global Assessment for Atopic Dermatitis

[a]MDA is defined as achieving 5 of the 7 following criteria: tender joint count ≤ 1; swollen joint count ≤ 1; Psoriasis Area and Severity Index ≤ 1 or body surface area $\leq 3\%$; patient pain visual analog scale score ≤ 15; patient global disease activity visual analog scale score ≤ 20; Health Assessment Questionnaire Disability Index ≤ 0.5; tender entheseal points ≤ 1

[b]Clinical remission per adapted Mayo score is defined as an adapted Mayo score ≤ 2, with a stool frequency subscore ≤ 1 and not greater than baseline, a rectal bleeding subscore of 0, and an endoscopic subscore ≤ 1

pregnancies during the clinical trials. The distribution of pregnancies across diseases was as follows: 34 with rheumatoid arthritis, 6 with psoriatic arthritis, 1 with non-radiographic axial spondyloarthritis, 23 with atopic dermatitis, 10 with ulcerative colitis, and 6 with Crohn's disease. One patient with rheumatoid arthritis had two pregnancies while on upadacitinib treatment. The first pregnancy ended in spontaneous abortion and approximately a year later, the patient became pregnant after reentering the study and had a live birth without congenital anomaly.

Given the frequent pregnancy testing mandated during clinical trials, a pregnancy was generally detected during the first trimester of pregnancy (< 13 weeks). In this analysis, gestational exposure ranged from 2 days to 19 weeks and

5 days gestation with the mean gestational age of in utero upadacitinib exposure of approximately 5 weeks and 3 days.

Pregnancy outcomes by disease indication are provided in Table 2. There were 43 live births reported: 42 live births without a congenital anomaly and one live birth with a congenital anomaly. Most of the live birth pregnancies were exposed to upadacitinib during the first trimester only with a mean gestational age of in utero upadacitinib exposure of 5 weeks and 5 days. There were two pregnancies with exposure beyond the first trimester, defined as > 13 weeks gestation. One infant (pregnant patient with non-radiographic axial spondyloarthritis) was exposed through 13 weeks and 2 days gestation and one infant (pregnant patient with atopic dermatitis) was exposed to upadacitinib through 19 weeks

Table 2 Summary of pregnancy outcomes with maternal exposure in upadacitinib clinical trials

	Rheumatoid arthritis ($n = 34$)	Psoriatic arthritis ($n = 6$)	nr-axial spondyloarthritis ($n = 1$)	Atopic dermatitis ($n = 23$)	Ulcerative colitis ($n = 10$)	Crohn's disease ($n = 6$)	Total ($N = 80$)
Live birth (without congenital anomaly)	18 (53%)	4 (67%)	1 (100%)	10 (43%)	6 (60%)	3 (50%)	42 (53%)
Live birth (with congenital anomaly)[a]	0	0	0	0	0	1 (17%)	1 (1%)
Spontaneous abortion	13 (38%)	1 (17%)	0	2 (9%)	1 (10%)	2 (33%)	19 (24%)
Still birth (no fetal defects)	0	0	0	0	0	0	0
Still birth (fetal defects)	0	0	0	0	0	0	0
Ectopic pregnancy	0	1 (17%)	0	0	0	0	1 (1%)
Elective termination (no fetal defects or unknown)	3 (9%)	0	0	11 (48%)	3 (30%)	0	17 (21%)
Elective termination (fetal defects)	0	0	0	0	0	0	0

nr non-radiographic

[a]One pregnancy resulted in a live birth with a congenital anomaly (atrial septal defect)

and 5 days gestation; both resulted in a live birth without congenital anomaly.

Of the 43 live births with known outcomes, one infant had a congenital anomaly, and three infants were born either premature or with complications. The live birth with a congenital anomaly was born to a 30-year-old patient in a Crohn's disease study who was in a state of clinical remission per the Crohn's Disease Activity Index (< 150) at the time of pregnancy. Exposure to upadacitinib was through 4 weeks and 4 days gestation. The patient had anemia and oligohydramnios during pregnancy and no complications during the delivery or postpartum period were reported. The male infant, born premature at 34 weeks and 5 days gestational age, had an atrial septal defect (ASD) diagnosed by an echocardiogram, a low birth weight of 2030 g (approximately ninth percentile based on prematurity [7–10]), neonatal transient tachypnea, hyperbilirubinemia, and septicemia. There was no family history of ASD and surgery was not required. No follow-up information was provided regarding spontaneous closure of the presumed ASD. Details of the additional three infants born either prematurely or with complications are further described in Table 3.

The 19 pregnancies resulting in a spontaneous abortion occurred in the following indications: rheumatoid arthritis (13), atopic dermatitis (2), Crohn's disease (2), ulcerative colitis (1), and psoriatic arthritis (1). Nine patients were taking concomitant methotrexate, a known abortifacient and allowed in some studies, at the time of awareness of the pregnancy. Of the ten patients without background methotrexate exposure, seven had other risk factors for spontaneous abortion, including advanced maternal age [> 35 years] ($n = 4$), type 1 diabetes mellitus ($n = 1$), and prior spontaneous abortion ($n = 2$). Overall, gestational exposure to upadacitinib among all patients experiencing spontaneous abortion occurred prior to 12 weeks gestation (mean exposure: 5 weeks and 2 days). Data on the timing of spontaneous abortions were limited, but for those with available information ($n = 10$), the median was approximately 8 weeks gestation.

Given the potential fetotoxic effects of methotrexate, further analysis was performed wherein patients were stratified based on the use of upadacitinib monotherapy versus upadacitinib with concomitant methotrexate in the upadacitinib clinical trials. Fifty-nine pregnancies occurred in patients receiving upadacitinib monotherapy, while 21 pregnancies occurred in patients receiving upadacitinib and methotrexate. Pregnancies on upadacitinib with concomitant methotrexate occurred in studies of patients with rheumatoid arthritis ($n = 19$) or psoriatic arthritis ($n = 2$). Overall outcomes of these pregnancies, stratified by upadacitinib monotherapy and upadacitinib with concomitant methotrexate, are provided in Fig. 1. Among 59 pregnancies reported in patients receiving upadacitinib monotherapy, there were 32 (54%) live births without a congenital anomaly, 1 (2%)

live birth with a congenital anomaly, 10 (17%) spontaneous abortions, and 16 (27%) elective terminations. Among 21 patients receiving upadacitinib with concomitant methotrexate, there were 10 (48%) live births without a congenital anomaly, 9 (43%) spontaneous abortions, 1 (5%) ectopic pregnancy, and 1 (5%) elective termination. There were no live births with a congenital anomaly in the upadacitinib with concomitant methotrexate group.

There were 17 elective terminations and none that reported fetal defects. The reasons provided for the elective terminations were mostly for family planning purposes and few were because of concerns of teratogenicity. One ectopic pregnancy occurred in a patient with psoriatic arthritis; this pregnancy occurred in the context of an intrauterine device, concomitant methotrexate use, and advanced maternal age of 40 years.

A breakdown of pregnancy outcomes by upadacitinib dose is presented in Table S4 in the ESM. Forty-five patients received upadacitinib 15 mg once daily and 31 received upadacitinib 30 mg once daily at the time of the positive pregnancy test. Four patients were on 6 mg twice daily, 12 mg twice daily, or 24 mg once daily and no patients were on upadacitinib 45 mg. Outcomes varied when stratified by dose with no clear patterns observed.

3.2 Postmarketing Pregnancy Cases and Outcomes

Postmarketing cases are voluntarily reported and, although proper diligence is performed by AbbVie to obtain the necessary follow-up, postmarketing cases often have missing or no information. Therefore, these cases are discussed separately from the clinical trial reports.

The cumulative total pregnancies reported via postmarketing surveillance was 211, in which there were 159 with unknown pregnancy outcomes and 52 pregnancies with known outcomes. Of the reports with known outcomes, a medical review revealed four pregnancy reports that described discontinuation of upadacitinib prior to pregnancy. These four unexposed pregnancies in addition to cases with unknown outcomes/ongoing at the time of data cutoff (163/211; 77%) were excluded from subsequent analyses.

In the 48 cases of known outcomes with maternal upadacitinib exposure, the majority were reported during treatment for rheumatoid arthritis ($n = 26$). This is not surprising as the rheumatoid arthritis indication received the first marketing authorization for use of upadacitinib in 2019. The remaining cases were reported during treatment for psoriatic arthritis ($n = 2$), ankylosing spondylitis ($n = 1$), atopic dermatitis ($n = 3$), ulcerative colitis ($n = 2$), and unknown indication(s) ($n = 14$). Fourteen cases were prospective (of which 11 are medically confirmed) and 34 were reported retrospectively. Based on the limited number of prospective and medically

Table 3 Summary of pregnant patients who delivered an infant preterm or with complications from clinical trial reports

	Maternal age, years	Disease state	Upadacitinib dose	Gestational exposure to upadacitinib	Concomitant therapies of interest	Additional case details
Premature infant born at 28 weeks gestation	32	Rheumatoid arthritis	30 mg QD	4 weeks and 2 days	No concomitant methotrexate or NSAID use Patient was receiving concomitant prednisone	Unknown reasons for prematurity
Premature infant born at 34 weeks gestation	34	Ulcerative colitis	15 mg QD	8 weeks and 3 days	No concomitant methotrexate use Patient was receiving daily aspirin	
Full-term infant with neonatal complications	27	nr-axial SpA	15 mg QD	13 weeks and 2 days	No concomitant methotrexate or NSAID use	Infant had mild respiratory distress due to slow reabsorption of alveolar lung fluid because of operative delivery (cesarean section) Infant received 30% oxygen for 24 h and was subsequently weaned to room air
Premature infant (34 weeks) with ASD diagnosed at birth	30	Crohn's disease	30 mg QD	4 weeks and 4 days	Patient was receiving numerous Chinese herbal medicines	Patient had anemia and oligohydramnios during pregnancy No complications during the delivery or post-partum period were reported Infant had an ASD diagnosed by an echocardiogram, low birth weight (2030 g), neonatal transient tachypnea, hyperbilirubinemia, and septicemia No family history of ASD Surgery was not required and no follow-up information was provided regarding spontaneous closure of ASD

ASD atrial septal defect, *nr-SpA* non-radiographic spondyloarthritis, *NSAID* non-steroidal anti-inflammatory drug, *QD* once daily

confirmed cases, prospective and retrospective cases were combined to present the totality of the data. Exposure timing to upadacitinib during gestation was not uniformly collected and missing in some cases; therefore, the exact weeks/days of gestational exposure could not be determined. However, the vast majority reported maternal exposure to upadacitinib was during the first trimester ($n = 32$) with only a few cases of unknown exposure timing ($n = 16$).

Postmarketing cases with known outcomes and exposure to upadacitinib ($n = 48$), composed of live births (22/48; 46%), spontaneous abortions (18/48; 38%), elective terminations (7/48; 15%), and ectopic pregnancy (1/48; 2%) are

Fig. 1 Pregnancy outcomes with maternal exposure in upadacitinib clinical trials stratified by concomitant methotrexate use. [a]Includes one infant born with a congenital anomaly (atrial septal defect). *SAB* spontaneous abortion
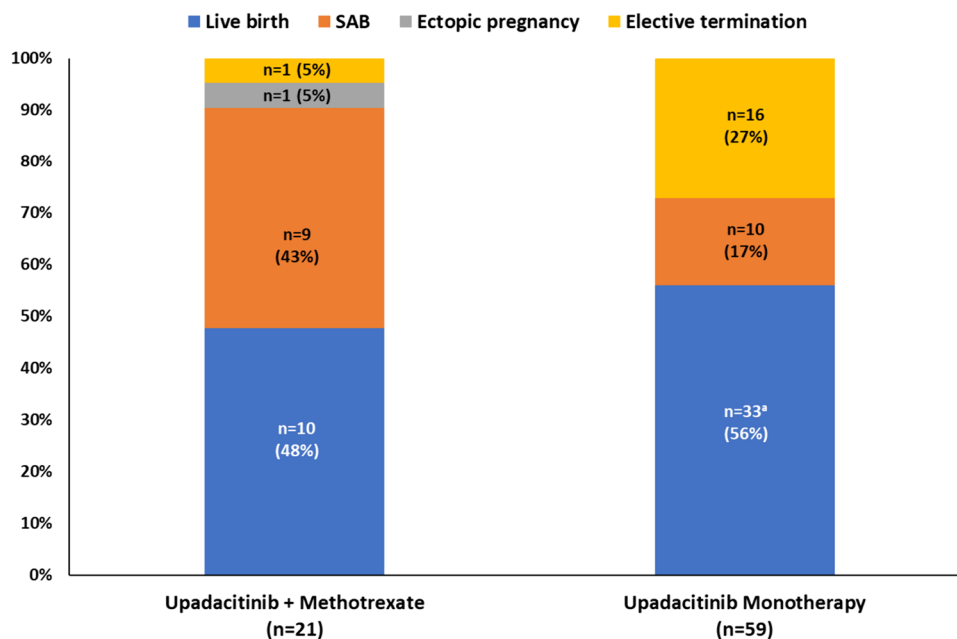
described here. Twenty-two live births without a congenital anomaly were reported, of which the majority were full term and had no neonatal complications. There were three premature infants (defined as <37 weeks gestation) and one infant of unknown gestational age considered large for gestational age. Further details on these four infants are provided in Table S5 of the ESM.

Eighteen (38%) spontaneous abortions were reported in patients with the following indications: rheumatoid arthritis ($n = 13$), atopic dermatitis ($n = 1$), ulcerative colitis ($n = 1$), psoriatic arthritis ($n = 1$), and unknown ($n = 2$). Risk factors reported that could have contributed to a miscarriage were as follows (some patients had multiple risk factors): five patients were of advanced maternal age at ≥ 35 years (three in the early 40s), two on concomitant methotrexate, three with current smoking history, one with adrenal insufficiency, one with uterine abnormalities, one with a history of prior spontaneous abortions, and eight who had no risk factors reported.

Seven elective terminations were reported, among which no fetal defects were documented. One ectopic pregnancy was reported in a patient with rheumatoid arthritis and no other information was provided.

4 Discussion

Chronic inflammatory autoimmune diseases often affect persons of childbearing potential. Persons with these conditions who succeed in getting pregnant may face challenges managing their underlying disease, as many approved treatments could affect pregnancy outcomes. In clinical trials for upadacitinib, 5234 persons of childbearing potential were treated with upadacitinib through 25 April, 2023. Despite an overall limited number of pregnancies occurring while on treatment, the prevalence of these conditions among persons of childbearing potential highlights the need to describe outcomes following exposures to upadacitinib during pregnancy.

At the time of pregnancy, more than half of the patients in upadacitinib clinical trials were in a state of remission, minimal disease activity, or inactive disease, with the exception of patients with ulcerative colitis (40% were in remission). Anecdotal evidence suggests that the impact of pregnancy on disease activity may vary by indication [11, 12]; however, research supports the notion that patients with autoimmune inflammatory diseases should aim to conceive during a period of inactive/controlled disease because the risk of a flare during pregnancy is reduced [13].

The exposure level at which malformations and/or embryo lethality are observed in embryofetal development studies influences the assessment of risk for human pregnancy [14]. Although upadacitinib is not genotoxic, it was teratogenic in preclinical animal studies equivalent to approved upadacitinib doses at therapeutic and subtherapeutic levels in human patients. Given the potential for human fetal risk with in utero exposure, highly effective methods of contraception were required in upadacitinib clinical studies to prevent pregnancy. Based on the embryofetal development data and the low exposure margins < 1-fold the human exposure at the maximum recommended human dose (45 mg), fetal risk and pregnancy prevention are outlined in worldwide labeling as a warning and precaution for in utero fetal exposure in the USA and a contraindication in pregnancy

in the European Union. Effective contraception measures and pregnancy testing are required as per the prescribing information.

All pregnancies have a background risk of congenital malformations, loss, or other adverse outcomes. In the US general population, the estimated background risk of major congenital malformations is 2–4% [1, 15, 16]. Across the available literature for clinical trials in patients with rheumatoid arthritis and psoriatic arthritis, the rate of observed congenital malformations is 2% [15, 16]. Reported rates are varied for patients with inflammatory bowel disease, with a few large studies showing no increased risk of congenital anomalies versus the general population, and a few small studies showing a slightly increased risk [17]. The rates of congenital anomalies observed with tofacitinib, another JAK inhibitor, in rheumatoid arthritis and psoriasis clinical trials was 2%, with none reported across 25 pregnancies from five clinical studies of tofacitinib in patients with ulcerative colitis [15, 18].

In this study, a single live birth among exposures to upadacitinib during pregnancy reported collectively during clinical trials and postmarketing surveillance resulted in a congenital anomaly. The anomaly was an ASD in a premature infant born to a mother enrolled in a Crohn's disease study. Atrial septal defect is the third most common congenital heart malformation [19] with recent epidemiologic data suggesting a prevalence of 1.6/1000 live births in the general population [20]. In clinical practice, observations of ASD and patent foramen ovale, a normal finding in preterm infants that can be misdiagnosed as ASD, are followed through the first 6 weeks of life because they often close spontaneously. The ASD reported in this study was noted upon examination at birth and no follow-up information was provided. No birth defects were reported among the elective terminations in clinical trials or postmarketing cases with known outcomes. Spontaneous abortions often occur early in gestation and cannot routinely be analyzed for congenital anomalies.

The 19 reports of spontaneous abortion in this study of the upadacitinib clinical program translate to an overall reporting rate of 24% (19 of 80 pregnancies); the rate of spontaneous abortion among patients receiving upadacitinib monotherapy was 17% (10 of 59 pregnancies) and 43% among pregnancies exposed to upadacitinib and methotrexate (9 of 21 pregnancies). In the US general population, the estimated risk of spontaneous abortion is approximately 15–20% [21]. Spontaneous abortion has been reported to be as high as 26% in studies across inflammatory diseases [22], with some evidence of increased risk compared with non-disease controls and a higher risk in those with advanced maternal age [15, 21] and higher disease activity (e.g., rheumatoid arthritis [22, 23], psoriasis [24], inflammatory bowel disease [25]). The existing literature on tofacitinib observed a spontaneous abortion rate of 19.4% among pregnancy outcomes in rheumatoid arthritis and psoriasis clinical trials [15]. Some upadacitinib studies allowed methotrexate as background concomitant therapy. Methotrexate is a therapy known to increase the risk of spontaneous abortion [5] and, when prescribed at higher doses than that typically used for the treatment of autoimmune inflammatory disease, may also be used for elective termination and termination of ectopic pregnancy [26, 27]. Indeed, previous studies have shown that patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors and methotrexate or leflunomide had higher spontaneous abortion rates than those receiving tumor necrosis factor inhibitor monotherapy (33% vs 24%) [28]; rates were also higher among patients with rheumatic diseases taking methotrexate postconception versus those who did not take methotrexate (42.5% vs 22.5%) [29]. In clinical trials, concomitant methotrexate use was reported in 26% (n = 21) of pregnancies with known outcomes, and the rate of spontaneous abortions among these patients on upadacitinib and concomitant methotrexate was 43% (9 of 21 pregnancies). Of the postmarketing cases, 18 spontaneous abortions represent 38% (18 of 48 pregnancies) of the total pregnancy reports with known outcomes.

Overall, this descriptive analysis suggests that frequencies of adverse pregnancy outcomes among patients exposed to upadacitinib during the first trimester of pregnancy were generally similar to corresponding percentages from published studies of pregnant women with inflammatory diseases, in particular rheumatic disease, and generally similar to the observed frequencies in the general population of pregnant women. The rate of congenital anomalies in upadacitinib clinical trials (none in postmarketing) was approximately 1% and comparable to the rate of major congenital anomalies estimated in the US general population (2–4%). The rate of spontaneous abortions in clinical trials in patients overall (24%), and then further stratified by those on upadacitinib monotherapy (17%) and those on upadacitinib and concomitant methotrexate (43%) was generally within the range of the reported background risk of 10–20% in the general population and no higher than rates from published studies of pregnant women with inflammatory diseases on concomitant methotrexate of 33–42.5%.

The relatively small number of clinical trial pregnancy reports overall may limit the interpretability of these data. Moreover, because the vast majority of maternal gestational exposure to upadacitinib in clinical trials and the postmarketing setting was limited to the early first trimester, no conclusions regarding longer or continued use of upadacitinib during pregnancy can be made. Limitations are inherent in the postmarketing data, including the difficulty in ascertaining pregnancy outcomes and the follow-up, small numbers of prospective documented cases, and a lack of exact gestational exposure timing. A review of postmarketing case

reports of pregnancy did not provide any additional insights on risk.

5 Conclusions

Preclinical findings of teratogenicity resulted in restrictive labeling regarding use in pregnancy. Because there are limited data in upadacitinib-exposed pregnancies, definitive conclusions cannot be drawn regarding the effect of upadacitinib on pregnancy outcomes. Based on a cumulative review of pregnancies during clinical trials and postmarketing surveillance to date, no apparent evidence of teratogenicity was found in the analyses of human pregnancies exposed to upadacitinib during the early first trimester. Rates of adverse pregnancy outcomes with upadacitinib exposure were comparable to rates observed in the general population or in patients with autoimmune inflammatory diseases not receiving upadacitinib. Pregnancy and infant outcomes will continue to be monitored during clinical trials and in the postmarketing setting via pharmacovigilance measures and a post-approval pregnancy study.

Declarations

sition of data: GL, HP. Data analysis: GL, HP. Interpretation of data: UM, LG, GL, MA, APL, LW, HP, TB-J, ML, MEBC, ABK, CC, ARS. Involved in drafting/revising critically for intellectual content: UM, LG, GL, MA, APL, LW, HP, TB-J, ML, MEBC, ABK, CC, ARS. All authors read and approved the final version.

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