AP&T Alimentary Pharmacology & Therapeutics WILEY

Multicentre study and systematic review: Allopurinol exposure during pregnancy

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Summary

Background: Data about the safety of allopurinol in pregnant women are sparsely reported.

Aims: To investigate the risk of adverse pregnancy outcome and congenital abnormalities after in utero exposure to allopurinol in inflammatory bowel disease (IBD) pregnancies and in general.

Methods: We collected safety data of patients with IBD who were treated with allopurinol during pregnancy between January 2013 and March 2022. Additionally, we performed a systematic review about the teratogenic potential of allopurinol.

Results: We collected data from 42 allopurinol-exposed pregnancies, including one twin pregnancy; in all women, allopurinol was combined with a thiopurine. Six

pregnancies (14.3%) resulted in miscarriage and one in stillbirth at 32 weeks. A congenital anomaly was observed in one newborn (coarctation of the aorta discovered postpartum). Three pregnancies, including the twin pregnancy, ended in moderate preterm delivery and one in very preterm delivery. Five neonates (15.2%) were small for gestational age. From our literature search, we identified an additional 102 allopurinol-exposed pregnancies resulting in 129 live births, including 36 infants from our cohort. Ten infants (7.8%) were born with a congenital anomaly. Two (1.6%) had a comparable pattern of multiple anomalies. The systematic review sub-analysis including only infants born to mothers with IBD (n = 76) revealed that 2.6% of infants had congenital anomalies after in utero exposure to a low dose of allopurinol.

Conclusions: Overall, the teratogenicity of allopurinol remains inconclusive. Children conceived by mothers treated for IBD with allopurinol/thiopurine co-therapy do not seem to have an increased risk of congenital anomalies.

1 | INTRODUCTION

Allopurinol, a xanthine oxidase inhibitor, was discovered five decades ago and is still widely used as treatment for gout and in the prevention of tumour lysis syndrome and recurrent nephrolithiasis.[1–4] It is also used in the management of autoimmune hepatitis (AIH) and inflammatory bowel disease (IBD) via the optimisation of the metabolism of immunomodulating therapy with thiopurines (azathioprine and mercaptopurine).[5–9] The addition of allopurinol to a thiopurine leads to a reduction of the potential toxic 6-methylmercaptopurine (6-MMP) levels and a concomitant rise in the pharmacologically active 6-thioguanine nucleotide levels.[6–8] Therefore, patients with a preferential metabolism towards 6-MMP can benefit from the addition of allopurinol to a reduced dose of the original thiopurine.[6] Moreover, it was recently shown that the remission rate in IBD was significantly higher in ulcerative colitis (UC) patients on azathioprine combined with allopurinol compared to azathioprine monotherapy (OR 2.54; 95% CI, 1.00–6.78; $p < 0.048$).[5] Because IBD incidence peaks in the second and third decades, and AIH also occurs during the reproductive years, many women wish to bear children, regardless of allopurinol treatment. Maternal and foetal safety of medication used during pregnancy is important and needs to be balanced with the potential risk of disease relapse. Especially considering that active disease is associated with adverse pregnancy outcomes.[10,11]

As allopurinol inhibits purine synthesis and hence may have direct effects on foetal dividing cells, the Food and Drug Administration stated that this drug should only be used during pregnancy when there is no safe alternative and when the disease itself carries risks for mother or child. A 2018 review, including a total of 53 first trimester allopurinol-exposed infants, concluded that the association between allopurinol and teratogenicity appears to be weak, but there were not enough cases to draw firm conclusions.[12] Since both the American Gastroenterological Association guideline and the European Crohn's and Colitis Organisation (ECCO) guideline highlights that the available data are insufficient, no recommendation can be made regarding its use during pregnancy, hence making it difficult to counsel women of fertile age/pregnant women.[10,11] To fill this gap in current knowledge about the use of allopurinol in pregnancy, the aim of the present multicentre study was to investigate the risk of adverse pregnancy outcome after maternal allopurinol use in combination with a systematic literature review about the potential teratogenicity of allopurinol during pregnancy.

2 | MATERIALS AND METHODS

2.1 | Study design

This multicentre study was performed from January 2013 to March 2022 in 11 centres in the Netherlands and one centre in Denmark. Moreover, the Pharmacovigilance Centre Lareb, a Dutch institute that identifies and reports adverse drug reactions, was approached for IBD cases. Patients were identified by their treating physician by personal recall and/or by quiring the local hospital database. They were included if diagnosed with Crohn's disease (CD), UC or IBD-unclassified and exposed to allopurinol during their pregnancy. Allopurinol exposure was defined as use of allopurinol at any given time during estimated time of conception and/or pregnancy. In some cases, the researchers were notified by the treating physician when patients became pregnant and data were collected prospectively, while in other cases the researchers were notified after the delivery and data were collected retrospectively.

2.2 | Maternal and IBD-related characteristics

The following patient characteristics were collected: age at delivery, smoking habits and alcohol consumption during conception or pregnancy, type of IBD, disease duration, daily dosage of allopurinol, co-medication and obstetric history.

2.3 | Pregnancy and neonatal characteristics

The following data on pregnancy and neonatal outcome were collected: disease activity during pregnancy, antibiotics-treated infections during pregnancy, obstetric complications (e.g. pregnancy induced hypertension, gestational diabetes, preeclampsia, HELLP [haemolysis, elevated liver enzymes and low platelets], hyperemesis gravidarum), mode of delivery, birthweight, gestational age at birth, Apgar scores (5 min), congenital anomalies and neonatal complications (i.e. neonatal infections, neonatal ward admission or neonatal intensive care unit admission including the reasons for admission).

Pregnancy loss before the 16th week was considered a miscarriage and after 16 weeks a stillbirth.[13] Very preterm birth was defined as birth before 32 weeks and moderate preterm birth as a birth between 32 and 37 weeks gestational age. Low birthweight was defined as a birthweight below 2500 g. In the Netherlands, small for gestational age (SGA) was defined as birthweight below the 10th percentile of the gestational age computed in the national pregnancy cohort.[14] In Denmark, this was defined as a birthweight of more than 2 standard deviations (SD) below the mean for children of similar gestation age, according to the reference curve of estimated foetal growth.[15] An Apgar score of less than 7 after 5 min was considered low and a score of 7 or higher was considered normal. In our manuscript, congenital anomalies were defined as structural or functional anomalies present at birth, with the exclusion of known chromosomal or genetic conditions. A flare in IBD disease activity during pregnancy was assessed by the treating physician and was based on either clinical symptoms, biomarkers or endoscopy.

2.4 | Statistical considerations

Categorical variables were described as numbers with percentages. Continuous variables were presented as means with SD or as medians with interquartile ranges (IQR1–IQR3), depending on their distribution. Normality was tested by visual inspection of histograms and with the Shapiro–Wilk test. All analyses were performed with SPSS statistics version 26 (IBM, Armonk, NY, USA).

2.5 | Systematic literature review and search

A systematic literature search was performed using the Embase and PubMed databases to collect publications before November 2022. The PubMed/Embase search strategy has been included as a File S1.

The search was restricted exclusively to human subjects and the reference lists of identified papers were cross-checked for additional relevant studies missed during the original search. Any original article, case report or conference abstract written in English or Dutch was eligible and there was no restriction in terms of publication date. Non-original articles and duplicates were excluded from this review.

After the search, the collected literature was screened on title and abstract by the first and last author for eligibility for full text evaluation. Disagreement regarding study eligibility was resolved by consensus between the first and last author. The same process was used for the full text screening. Studies that included women who took allopurinol at any time during pregnancy for a maternal indication such as gout, AIH or IBD, and reported foetal outcomes were included. Studies in which allopurinol was used for a foetal indication, for example, reduction of hypoxic–ischemic brain injury, cardioprotective effect, placental dysfunction, were excluded. Also, studies that only reported maternal outcomes or did not mention anything about congenital anomalies in live born children were not eligible for inclusion. The primary outcome of our review was the number and type of congenital anomalies. The secondary outcomes were other adverse pregnancy outcomes.

3 | RESULTS

3.1 | Maternal characteristics

We identified 42 pregnancies (41 singleton and 1 twin pregnancy) in 31 women with IBD, including four pregnancies previously mentioned by Julsgaard et al.[16,17] Required additional data was provided by the treating physician for these four previously described pregnancies. In 35 (83%) pregnancies, data were collected retrospectively and in seven (17%) pregnancies prospectively.

A thiopurine in combination with daily allopurinol was used by all women during the first trimester. Maternal characteristics are shown in Table 1.

3.2 | Pregnancy complications

Obstetric complications were observed in seven pregnancies (17%). One patient was admitted at week 40 for fever caused by influenza type A virus, after which it was decided to induce labour. Obstetrical outcomes are shown in Table 2.

Seven (17%) women, all but one diagnosed with UC, experienced a disease relapse. Watchful waiting was chosen in two cases, and no alterations to medical treatment was needed. In the other five cases treatment was started with 25 mg of oral prednisone (n = 1), oral budesonide (n = 1), oral mesalamine (n = 1), shortening the infliximab interval (n = 1) or by restarting, 15 weeks after the discontinuation, azathioprine with allopurinol at 24-week gestational age (n = 1).

Six pregnancies (14.3%) resulted in a first trimester miscarriage after a median of 8 weeks and 4 days (IQR 8–10 weeks). One pregnancy resulted in a still birth at 32 weeks. During this pregnancy, the patient developed disease activity at week 27 for which treatment with oral prednisolone 25 mg daily was started. At 32 weeks, there

TABLE 1 Maternal characteristics of allopurinol-exposed pregnancies (n=42).

Dutch cohort	34 (81%)
Dutch Pharmacovigilance Centre Lareb	2 (5%)
Danish cohort	6 (14%)
Age at delivery in years, mean (SD)	30 (5.1)
Disease duration in years, median (IQR)	6 (3–8)
Inflammatory bowel disease subtype, n (% of cases):	
Ulcerative colitis	9 (21)
Crohn's disease	33 (79)
Previous IBD surgery, n (% of cases)	3 (7.1)
Smoking, n (% of cases)	
Yes	3 (7)
No	31 (74)
Missing	8 (19)
Multiparous, n (% of cases)	22 (52)
Previous miscarriage, n (% of cases)	10 (24)
Allopurinol used during pregnancy, n (% of cases)	
Conception and First trimester	42 (100)
Second trimester	32 (76)
Third trimester	32 (76)
Throughout pregnancy	31 (74)
Daily dosage of allopurinol in milligram, median (IQR)	100 (100–100)
Type of thiopurine, n (% of cases)	
Azathioprine	19 (45)
Daily dosage in milligram, median (range)	50 (50–75)
Mercaptopurine	17 (41)
Daily dosage in milligram, median (range)	25 (25–50)
Unknown	6 (14)
IBD co-medication during first trimester, n (% of cases)	42 (100)
Thiopurine	42 (100)
Oral mesalazine	8 (19)
Anti-TNF-α	9 (21)
Vedolizumab	2 (5)
Other	2 (5)
IBD co-medication during second trimester, n (% of cases)	36 (100)
Thiopurine	35 (97)
Oral mesalazine	8 (22)
Anti-TNF-α	8 (22)
Vedolizumab	2 (6)
Oral prednisone	1 (3)
Other	2 (6)
IBD co-medication during third trimester, n (% of cases)	36 (100)
Thiopurine	35 (97)

TABLE 1 (Continued)

Oral mesalazine	8 (22)
Anti-TNF-α	6 (17)
Vedolizumab	2 (6)
Oral prednisone	1 (3)
Oral budesonide	1 (3)
Other	2 (6)

Abbreviations: Anti-TNF-α, anti-tumour necrosis factor-α; IBD, inflammatory bowel disease; IQR, interquartile range; SD, standard deviation.

was a foetal demise after which labour was induced, resulting in a stillborn baby with a weight normal for gestational age (1970 g) without any congenital malformations. Placental examination did not reveal the cause of foetal death, and no further investigations were performed.

In 14 of the 35 completed pregnancies (40%), a caesarean section was performed; seven were elective and seven were performed in an emergency setting. The indication for an elective caesarean were: perianal disease (n=3), previous caesarean section (n=1), breech position (n=2) and on advice of the gastroenterologist (n=1). The indications for an emergency caesarean were: foetal distress (n=3), obstructed labour (n=2) and severe preeclampsia (n=2).

3.3 | Foetal and neonatal outcomes

Three pregnancies, including the twin pregnancy, ended in a moderate preterm delivery (range 32–35+6 weeks) and one in a very preterm delivery (28 weeks). In none of these pregnancies did the mother have a disease flare during pregnancy. The five children born preterm had a median birthweight of 2145 gram (range 1030–2680 g), and one was SGA (singleton pregnancy). During four additional singleton pregnancies, the offspring were also SGA. In one of these pregnancies, a flare occurred at gestational week 28, and was resolved with oral budesonide. One neonate was born with a congenital anomaly (coarctation of the aorta). During pregnancy this neonate was exposed to infliximab and azathioprine in combination with allopurinol and no genetic cause was detected. Neonatal characteristics are provided in Table 2.

Six newborns (17%) were admitted to the neonatal ward for various reasons (Table 2). On day two after delivery, one newborn, initially admitted due to hypoglycaemia and hypotonia was transferred to the neonatal intensive care unit due to respiratory distress syndrome.

In 30 (86%) of 35 completed pregnancies, allopurinol was continued during the postpartum period. Overall, 12 (40%) offspring of mothers on allopurinol were breastfed for an unspecified period, without any reports of adverse infant outcomes based on maternal information provided to their treating gastroenterologist. The reasons for not breastfeeding in the remaining 18 (60%) cases were not reported.

TABLE 2 Pregnancy complications and outcomes of 42 women who received allopurinol during pregnancy.

	Singleton pregnancies (n = 41)	All pregnancies including 1 twin pregnancy (n = 42)
Complications		
PIH, n (% of cases)	1 (2.4)	1 (2.4)
Gestational diabetes, n (% of cases)	2 (4.9)	2 (4.8)
Pre-eclampsia (including HELLP), n (% of cases)	4 (9.8)	4 (9.5)
Hyperemesis gravidarum, n (% of cases)	0 (0)	0 (0)
Infectious maternal complications during pregnancy which required hospitalisation or antibiotics, n (% of cases)	1 (2.4)	1 (2.4)
Influenza type A virus	1 (2.4)	1 (2.4)
Pregnancy outcomes		
Miscarriage, n (% of cases)	6 (15)	6 (14)
Stillbirth, n (% of cases)	1 (2)	1 (2)
Number of live born children	34 (83)	36 (84)
Gestational age in weeks, median (IQR)	39 (38–40)	39 (38–40)
Birth weight (g), median (IQR)	3375 (2970–3800)	3320 (2807–3743)
Preterm birth, n (% of cases)		
Very preterm <32 weeks GA	1 (3)	1 (3)
Moderately preterm 32–36 weeks GA	2 (6)	3 (9)
Low birthweight (<2500 g), n (% of cases)	2 (6)	4 (11)
Small for gestational age, n (% of cases)	5 (16.1, n = 31)	5 (15.2, n = 33)
Congenital anomalies in live born children, n (% of cases)	1 (3)	1 (2.8)
APGAR score <7 after 5 min, n (% of cases)	0 (0, n = 29)	0 (0, n = 31)
Caesarean section, n (% of cases)	14 (41)	14 (40)
Infant admission to neonatal ward or neonatal intensive care unit		
Neonatal ward admission, n (% of cases)	6 (18)	6 (17)
Reasons for neonatal ward admission, n (% of cases)[a]		
Prematurity	1 (3)	1 (3)
Glucose monitoring/ neonatal hypoglycaemia[b]	5 (15)	5 (14)
Jaundice	1 (3)	1 (3)
Hypotonia	1 (3)	1 (3)
Neonatal intensive care admission, n (% of cases)	1 (3)	1 (3)
Reasons for neonatal intensive care admission, n (% of cases)		
Respiratory distress syndrome	1 (3)	1 (3)

Abbreviations: HELLP, haemolysis, elevated liver enzymes and low platelets; IQR, interquartile range; PIH, pregnancy-induced hypertension.

[a]Some infants were admitted for more than one reason.

[b]Infant was initially admitted at the neonatal ward admission due to hypoglycaemia and hypotonia but later transferred to the neonatal intensive care unit due to respiratory distress syndrome.

3.4 | Results systematic literature review

The search strategy yielded 693 articles and nine articles were identified from citation searching. After removing duplicates 583 articles were screened for title and abstract. Of the 80 articles selected for full-text review, 28 were included in this study. In order to avoid duplicates, the two studies with the total of four cases included in the present multicentre study were excluded from the review.[16,17] The selection process is depicted in Figure 1.

3.5 | Allopurinol exposure during pregnancy: Review of all cases

A total of 102 allopurinol-exposed pregnancies have been described in the literature (Table 3). Together with the 42 pregnancies in this cohort, we collected data of 144 allopurinol-exposed pregnancies. Allopurinol was used in varying dosages (range 50–600 mg/day) for different indications such as IBD, gout, related hyperuricaemia conditions and leukaemia. These pregnancies

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources
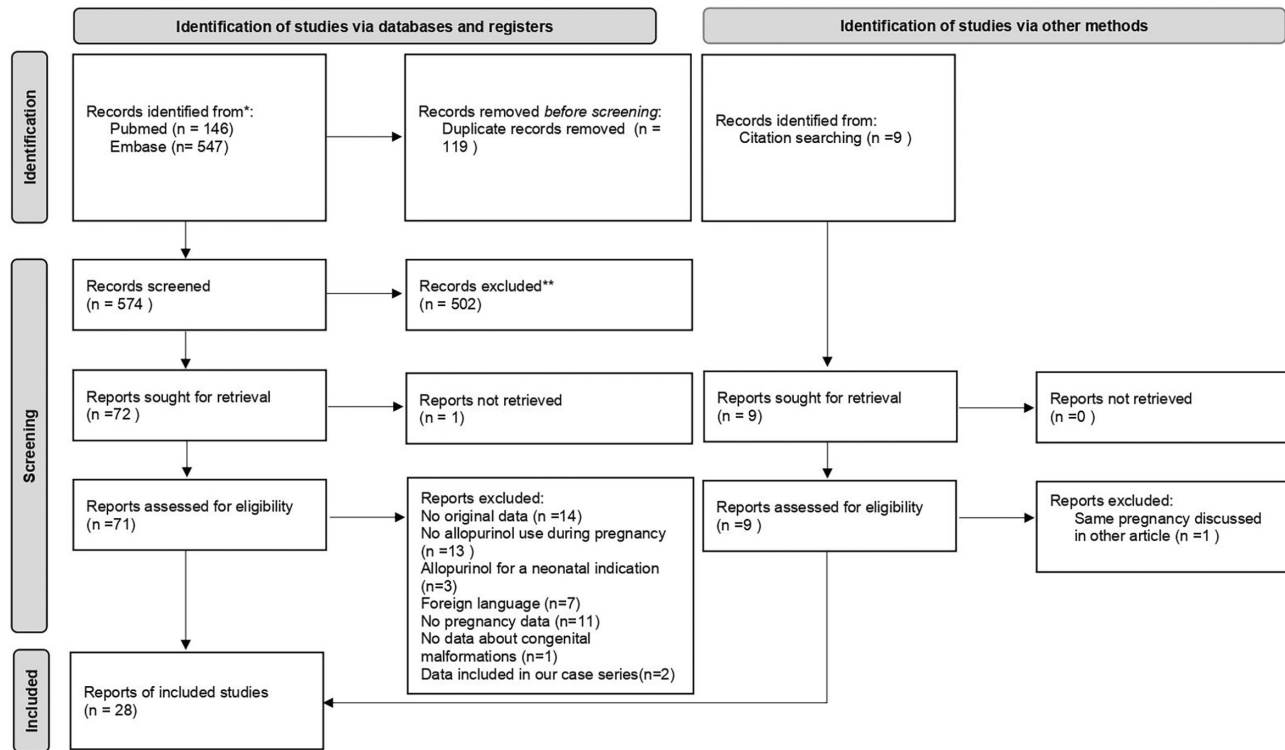
FIGURE 1 Flow chart of study selection.

resulted in 129 live births (including three twin pregnancies), 12 miscarriages (8%), three stillbirths (2%) and three elective abortions (2%). A preterm birth occurred in 17% of pregnancies ($n = 20/120 +$ missing data in 6 cases) and 14% ($n = 13/91 +$ missing data in 38 cases) of infants were born with a low birthweight. Ten infants (7.8%) were born with one or more congenital anomalies (Table 3 and Table S1), one with an inborn error of metabolism (phenylketonuria) and one with a genetic disorder (congenital hypoparathyroidism).[18–22] There was no clear correlation between pregnancy outcome and disease type (Table S1). The median daily maternal allopurinol dosage in the infants with a congenital anomaly was 100 mg (range 100–400 mg). Except for two infants, only exposed in the second and third trimester, all other congenital anomalies occurred in infants at least exposed to allopurinol in the first trimester ($n = 8$; Table 3). The percentage of reported congenital anomalies was lower among low-dose allopurinol exposure (≤100 mg/day, as prescribed in IBD pregnancies: $n = 6/58$ [10.3%]) compared with a high dosage ($n = 4/15$ [26.7%]). Of note, a high percentage of missing data in relation to allopurinol dosage in pregnancy was reported ($n = 56/129$ [43.4%]).

Two infants had a comparable pattern of major external and internal malformations including ocular (microphthalmia), orofacial (cleft lip and palate, auditory and mandibular abnormalities),

urogenital and gastrointestinal defects.[20,23] In one pregnancy the mother was treated with allopurinol 300 mg/day for recurrent kidney stones for at least 12 years.[23] Her remaining medications included multivitamins and methyldopa, which are not considered to be teratogenic.[23,24] The second mother had hyperoxaluria and was, in addition to allopurinol 100 mg/day, treated with hydrochlorothiazide and pyridoxine, both not considered as teratogens.[20,25] Both infants had a normal foetal karyotype (46,XY), but further genetic analysis was not performed.[20,23] In the other eight infants, the congenital anomalies were present in different systems, but most were in the musculoskeletal (1× inguinal hernia and 2× umbilical hernia) and circulatory system (1× coarctation of the aorta, 2× patent foramen ovale, 1× pulmonary artery stenosis, 2× patent ductus arteriosus, 1× small pericardial effusion, increased flow velocity, small right ventricular dilatation and a patent ductus arteriosus aneurysm, compatible with cardiac insufficiency).[18,20–22]

Overall, 76 (59%) of the 129 allopurinol-exposed infants were born to mothers with IBD, all but one were treated with allopurinol 100 mg/day or less and all combined with a thiopurine. In this IBD-cohort, two infants were born with a congenital anomaly (2.6%), an inguinal hernia and a coarctation of the aorta, respectively. In the non-IBD cohort, there was a congenital anomaly rate of 15.1% (8 of 53 cases).

TABLE 3 Overview of the published studies meeting the eligibility criteria of the systematic literature review.

Study, year and design	Patient characteristics	Treatment indication	Allopurinol dosage	Co-medication during pregnancy	Birth outcomes	Congenital anomalies or genetic disorders	Low birthweight (<2500g)	Preterm delivery (<37 weeks)
Ali et al.[45] 2009, case report	36 y/o woman	B-cell chronic lymphocytic leukaemia	300mg/day, stopped at week 20	Chlorambucil	Healthy infant, CS	None	Yes, 2235g	Yes, 36weeks. CS for a maternal indication (preeclampsia)
AlKindi et al.[46] 2005, case report	27 y/o woman	Philadelphia positive chronic myeloid leukaemia	Unknown, started at week 28 of pregnancy	Interferon alfa	Healthy infant	None	Unknown	Unknown
Awidi et al.[47] 1983, case report	32 y/o woman	Acute leukaemia	300mg/day, started at week 17 of pregnancy	Adriamycin, vincristine, prednisolone, l-asparaginase, cyclophosphamide, methotrexate, mercaptopurine	Healthy infant	None	No, 3200g	No, approximately 38weeks
	28 y/o woman	Acute leukaemia	300mg/day, started at week 24 of pregnancy	Adriamycin, cytosine arabinoside, thioguanine	Healthy infant	None	No, 2980g	Yes, approximately 36weeks
Belli et al.[48] 2009, case report	Unknown	Unknown	Unknown	Oral contraceptive, NSAID's	Elective abortion	–	–	–
Beswick et al.[33] 2016, case series	23 pregnancies in 19 women. Median age 32 y (range 25–37)	9 Crohn's disease and 10 ulcerative colitis	Unknown	Thiopurines	22 live births, 1 miscarriage, 1 foetal death at 25weeks.	None	Besides in 1 twin pregnancy, no LBW infants	Besides in 1 twin pregnancy, no spontaneous preterm deliveries
Boros et al.[18] 1977, case report	26 y/o woman	Chronic granulocytic leukaemia	400mg/day started at week 20 and stopped at week 37 of pregnancy	Busulfan	Infant with a congenital anomaly	Right renal agenesis. Moreover the infant suffered from hydronephrosis of the left kidney and hepatic subcapsular calcifications	Yes, 2101g	No, 39 weeks
Brown et al.[49] 2001, case report	27 y/o woman	Non-Hodgkin's lymphoma	Unknown, started at week 16 and stopped at week 34 of pregnancy	Cyclophosphamide, doxorubicin, vincristine, prednisone	Healthy infant, VD	None	No, 3043 gram	No, 37 weeks
Coddington et al.[50] 1979, case report	30 y/o woman	Gout	300mg/day	Iron, multivitamins	Healthy infant	None	Appropriate for gestational age	Yes, 35+5weeks. SROM
Dhonnchu et al.[51] 2012, case report	33 y/o woman	Heart, lung and renal transplant due to CF	Unknown	Tacrolimus, trimethoprim-sulphamethoxazole, colistin sulphomethate sodium, azithromycin, simvastatin, ursodeoxycholic acid, calcium carbonate, darbepoetin alfa, lansoprazole, pancrelipase capsules, folinic acid	Healthy infant, CS	None	Yes, 2450g	Yes, 34+5weeks. CS for a maternal indication (atrial fibrillation)
Farber et al.[19] 1976, case report	23 y/o woman	Glycogen storage disease type 1b	300mg/day, stopped in first trimester	Ampicillin, oral and parenteral iron	Infant with an inborn error of metabolism, CS	Phenylketonuria	No, 3345g	No, a term

(continues)

TABLE 3 (Continued)

Study, year and design	Patient characteristics	Treatment indication	Allopurinol dosage	Co-medication during pregnancy	Birth outcomes	Congenital anomalies or genetic disorders	Low birthweight (<2500g)	Preterm delivery (<37 weeks)
Fazal et al.[22] 2013 case series	29 y/o woman	Ulcerative colitis	100mg/day	Azathioprine	Infant with a congenital anomaly, CS	Inguinal hernia	No, 3000g	No, 37 weeks
	29 y/o woman	Ulcerative colitis	100mg/day	Azathioprine, prednisolone, folate	Healthy infant, CS	None	Unknown	No, a term delivery
	28 y/o woman	Crohn's disease	100mg/day	Azathioprine, adalimumab	Healthy infant, CS	None	Unknown	No, 38weeks
Grünert et al.[52] 2022, case report	35 y/o woman	Glycogen storage disease type 1b and kidney stones	Unknown, stopped at week 5 of pregnancy	Empagliflozin, phenprocoumon, enoxaparin	Healthy infant, CS	None	No, 2940g	No, 37 weeks
Hoeltzenbein et al.[20] 2013 prospective cohort	Unknown details	Renal transplantation	Range 50-600mg/day	Mycophenolate, cyclosporine various antihypertensives	SAB	–	–	–
	Unknown details	Unknown	Range 50-600mg/day	Valsartan, hydrochlorothiazide	SAB at week 20 due to chorioamnionitis	None	–	–
	Total of 2 woman	Unknown	Range 50-600mg/day	Unknown	2 elective abortions	–	–	–
	Total of 5 woman	Unknown	Range 50-600mg/day	Unknown	5 premature infants	None	Unknown	Yes, 5 premature infants
	Total of 16 woman	Unknown	Range 50-600mg/day	Unknown	16 healthy infants	None	Unknown	No, a term delivery
	Unknown details	Hyperuricaemia	100mg/day, stopped at week 5+2 of pregnancy	Ramipril, metoprolol, alpha-methyldopa, hydrochlorothiazide, amlodipine, simvastatin, metformin, venlafaxine, tilidine, naloxone, paracetamol, acetylsalicylic acid, insulin, insulin lispro	Infant with congenital anomalies	Patent foramen ovale, pulmonary artery stenosis (hemodynamically not relevant)	Unknown	No, 37+2weeks
	Unknown details	Glomerulonephritis	100mg/day, stopped at week 8+2 of pregnancy	Amlodipine, valsartan, metoprolol, hydrochlorothiazide, alpha-methyldopa, desloratadine	Infant with congenital anomalies	Small patent ductus arteriosus, mild ptosis right eye, umbilical hernia	Unknown	Yes, 29+2weeks
	Unknown details	Hyperuricaemia	50mg/day, stopped at week 9+3 of pregnancy	Calcitriol	Infant with a genetic disorder	Congenital hypoparathyroidism (autosomal-dominant)	Unknown	Yes, 36+6weeks
	Unknown details	Gout	300mg/day, stopped at week 14 of pregnancy	Furosemide, pravastatin, cerivastatin	Infant with congenital anomalies	Haemangioma	Unknown	No, 38 weeks

TABLE 3 (Continued)

Study, year and design	Patient characteristics	Treatment indication	Allopurinol dosage	Co-medication during pregnancy	Birth outcomes	Congenital anomalies or genetic disorders	Low birthweight (<2500g)	Preterm delivery (<37 weeks)
	Unknown details	Haemolytic uremic syndrome	100mg/day	Alpha-methyldopa, metoprolol, moxonidine, furosemide clonidine, darbepoetin alfa, danaparoid, enoxaparin, corticosteroids, colecalciferol, alfacalcidol	Infant with congenital anomalies	Persistent ductus arteriosus, patent foramen ovale, umbilical hernia	Unknown	Yes, 28weeks
	Unknown details	Hyperoxaluria type 1	100mg/day	Hydrochlorothiazide, sodium carbonate, pyridoxine	Infant with multiple congenital anomalies	Cleft lip and palate (left), low-set ears, conductive deafness, retrognathia, microphthalmia, hepatosplenomegaly/cholestasis, renal hypoplasia, bilateral cryptorchidism, micropenis, enlargement of ventricles, osteopenia	Unknown	No, 37+3weeks
Khan et al.[53] 2021, case report	20 y/o woman	Gout and CKD	300mg/day stopped at week 5 of pregnancy. Restarted 200mg/day at week 16 due to acute uric acid nephropathy	Unknown	Healthy infant	None	Unknown	Unknown
	23 y/o woman	Gout and CKD	300mg/day	Unknown	Healthy infant	None	Unknown	Unknown
Kozenko et al.[23] 2011, case report	35 y/o woman	Nephrolithiasis	300mg/day	Multivitamins, methyldopa	Infant with multiple congenital anomalies, died on day 8 of life, CS	Hypertelorism, left-sided microphthalmia, colomba involving the upper eyelid, left-sided microtia, absent left external auditory canal, simplified right ear with a preauricular tag, left-sided cleft lip, cleft palate, undescended testes bilaterally, hypoplasia of the corpus callosum, left optic nerve atrophy, left microphthalmia, small frontal fossa, agenesis of the left diaphragm with intrusion of the liver, stomach and spleen into the diaphragmatic space, mildly enlarged right-sided kidney, absent left kidney, small accessory spleen and profound left pulmonary hypoplasia	No, 3593g	No, 41weeks

TABLE 3 (Continued)

Study, year and design	Patient characteristics	Treatment indication	Allopurinol dosage	Co-medication during pregnancy	Birth outcomes	Congenital anomalies or genetic disorders	Low birthweight (<2500g)	Preterm delivery (<37 weeks)
Krueger et al.[54] 1976, case report	15 y/o woman	Acute lymphocytic leukaemia	Unknown	Acetazolamide, prednisone, vincristine, mercaptopurine, cyclophosphamide, cytarabine, intrathecal methotrexate	Healthy infant, VD	None	No, 2963g	No, 38weeks
Levin et al.[55] 2017, case report	22 y/o woman	Glycogen storage disease type 1b	Unknown, stopped early in first trimester	Tranexamic acid, penicillin, ceftriaxone	Infant needed NICU admission for respiratory distress and hypoglycaemia, cs	None	No, 2500 g	No, 37 weeks
Lhotta et al.[56] 2009, case report	23 y/o woman	Familial juvenile hyperuricaemic nephropathy. Hyperuricaemia, gout and chronic kidney disease	150mg/day in second and third trimester	Calcitriol, EPO	Healthy infant	None	Unknown	No, at term
Martens et al.[57] 2008, case report	34 y/o woman	Glycogen storage disease type 1a	Unknown	Unknown	Healthy infant	None	No 3530g	No, 38+4weeks
	31 y/o woman	Glycogen storage disease type 1a	Unknown	Unknown	Healthy infant	None	No 3260g	No, 38+3weeks
O'Donnel et al.[58] 1979, case report	34 y/o woman	Acute myeloblastic leukaemia	300mg/day started at week 27	Thioguanine, cytosine arabinoside, daunorubicin	Healthy infant, VD	None	No, 5000g	No, approximately 40weeks
	24 y/o woman	Acute lymphoblastic leukaemia	300mg/day started at week 15	Thioguanine, cytosine arabinoside, daunorubicin	Intra-uterine death at 29 weeks, mother diagnosed with severe PE.	None (although karyotyping was not performed)	-	-
Paci et al.[59] 2009, case report	24 y/o woman	Glycogen storage disease type 1b	Unknown, stopped in pregnancy	Unknown	Healthy infant	None	No, appropriate for gestational age	No, 40weeks
Podolská et al.[60] 2022, retrospective cohort	1 woman, 3 pregnancies, unknown age	Unknown	300mg/day	Prednisone, nadroparin, fluvastatin	3x SAB	—	—	—

TABLE 3 (Continued)

Study, year and design	Patient characteristics	Treatment indication	Allopurinol dosage	Co-medication during pregnancy	Birth outcomes	Congenital anomalies or genetic disorders	Low birthweight (<2500g)	Preterm delivery (<37 weeks)
Sechi et al.[61] 2012, retrospective cohort	A total of 3 woman	Glycogen storage disease type 1a or type 1b	Unknown, stopped during pregnancy	Unknown	3 healthy infants	None	Unknown	Unknown
Sheikh et al.[34] 2015, retrospective cohort	21 y/o woman	Ulcerative colitis	100mg/day	Azathioprine, omeprazole, pentasa, ferrous fumarate, ascal	Healthy infant, VD	None	No, 3500 g	No, 41 weeks
	24 y/o women	Ulcerative colitis	100mg/day	Azathioprine, pentasa	Healthy infant, CS	None	No, 2900 g	No, 38 weeks
	34 y/o women	Ulcerative colitis	100mg/day	Azathioprine	Healthy infant, CS	None	No, 3400 g	No, 39 weeks
	31 y/o women	Ulcerative colitis	200mg/day	Azathioprine, ferrous fumarate	Healthy infant, VD	None	No, 4000 g	No, 40 weeks
	30 y/o women	Ulcerative colitis	100mg, 5 d/wk	Mercaptopurine, balsalazide	Healthy infant, VD	None	No, 3800 g	No, 38 weeks
	36 y/o women	Ulcerative colitis	100mg, 5 d/wk	Mercaptopurine, mesalazine	Healthy infant, VD	None	No, 3000 g	No, 39 weeks
	32 y/o women	Ulcerative colitis	100mg, 3 d/wk	Mercaptopurine, cyclosporine, ferrous fumarate	Healthy infant, CS	None	No, 2900 g	Yes, 36 weeks
	29 y/o women	Crohn's disease	100mg, 6 d/wk	Mercaptopurine, ferrous fumarate	Healthy infant, CS	None	No, 3500 g	No, 38 weeks
	34 y/o women	Crohn's disease	100mg, 4 d/wk	Mercaptopurine, adalimumab, ferrous fumarate	Healthy infant, VD	None	No, 3400 g	No, 38 weeks
	29 y/o women	Crohn's disease	100mg, 4 d/wk. Stopped at month 6	Mercaptopurine	Healthy infant, VD	None	No, 3100 g	No, 38 weeks
	32 y/o women	Ulcerative colitis	100mg, 5 d/wk	Mercaptopurine, ferrous fumarate	Healthy infant, CS	None	No, 3100 g	No, 38 weeks
	32 y/o women	Ulcerative colitis	100mg, 5 d/wk	Mercaptopurine, balsalazide	Healthy infant, VD	None	No, 3800 g	No, 39 weeks
	31 y/o women	Ulcerative colitis	100mg, 4 d/wk	Mercaptopurine, mesalazine	Twin pregnancy complicated by TTTS, one of them died 13 weeks post delivery	None	Yes, <400 g	Yes, 25 weeks

(continues)

TABLE 3 (Continued)

Study, year and design	Patient characteristics	Treatment indication	Allopurinol dosage	Co-medication during pregnancy	Birth outcomes	Congenital anomalies or genetic disorders	Low birthweight (<2500g)	Preterm delivery (<37 weeks)
Theodora et al.[21] 2019, case report	26 y/o woman	B-cell acute lymphoblastic leukaemia	300mg/day, started at week 23	Dexamethasone, doxorubicin, filgrastim, vincristine	Infant with a congenital anomaly, CS	Small pericardial effusion, increased flow velocity, small right ventricular dilatation and a patent ductus arteriosus aneurysm, compatible with cardiac insufficiency	Yes, 1670 g	Yes, 31 + 4 weeks
Seinen et al.[62] 2012, case report	25 y/o woman	Ulcerative colitis	100mg/day	Mercaptopurine, mesalazine, topical mesalazine	Healthy infant, elective CS	None	No, 3550 g	No, 39 weeks
Van Veen et al.[63] 2015, case report	37 y/o woman	Gout	Unknown, stopped at pregnancy confirmation and restarted at 34 weeks	Hydrocodone, glyburide	Healthy infant, VD	None	No, 3811 g	No, 39 weeks
Yadav et al.[64] 2013, case report	30 y/o woman	Chronic myeloid leukaemia	300mg/day, started at 32 weeks of pregnancy	Hydroxyurea, imatinib	Healthy infant, elective CS	None	Yes, 2000g	No, 37 weeks

Abbreviations: CF, cystic fibrosis; CKD, chronic kidney disease; CS, caesarean section; EPO, erythropoietin; LBW, low birthweight; NICU, neonatal intensive care unit; NSAID, non-steroidal anti-inflammatory drug; PE, pre-eclampsia; SAB, spontaneous abortion; SROM, spontaneous rupture of the membranes; TTTS, twin to twin transfusion syndrome; VD, vaginal delivery.

4 | DISCUSSION

This multicentre study and systematic review is the largest study to date comprehensively examining risk of adverse pregnancy outcome after allopurinol use in pregnancy. The present study in IBD-pregnancies and the systematic review sub-analysis in IBD-pregnancies revealed a relatively low risk of congenital malformations after in utero exposure to a relatively low dose of allopurinol in pregnancy. However, the overall risk of congenital malformations comprising all types of patients exposed to allopurinol in variable dosage in pregnancy resulted in congenital malformations in nearly one in 13 live-born infants. Further, overall, one in six infants were born preterm, although the risk was lower in the sub-population of IBD patients.

Since allopurinol inhibits purine synthesis it may have a direct effect on dividing cells in utero.[26] Studies about the teratogenicity of allopurinol in animals have shown variable results.[27,28] One animal study reported skeletal abnormalities, a cleft palate or a harelip in mice embryos exposed to a large dose (50 or 100mg/kg) of intraperitoneal allopurinol,[27] while studies in other species reported no foetal harm.[28] Even though the congenital anomaly rate in our systematic review (7.8%) is high, it is comparable to the congenital anomaly rate among all live births from mothers with IBD of 9% found in the large, prospective Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry.[29,30] In contrast, the EUROCAT registry (European network of population-based registries for the epidemiologic surveillance of congenital anomalies), a registry that covers about 25% of the European birth population, reported in 2019 a major congenital anomalies rate (excluding genetic anomalies) of 2.1% in all cases.[31] We speculate the higher overall risk found in our review compared to the European population, might partially be explained by maternal comorbidity, although a clear correlation between pregnancy outcome and disease type was lacking (Table S1). Moreover, it is very likely that there is an over-reporting in literature of cases with congenital anomalies and an underreporting of uneventful allopurinol-exposed pregnancies, given the scarcity of allopurinol-related pregnancy data over the many decades that allopurinol has been used.

When specifically looking at IBD pregnancies, our cohort study and the systematic review sub-analysis in IBD-pregnancies revealed that 2.8% and 2.6% of infants had congenital anomalies after in utero exposure to a low dose of allopurinol, respectively. This relatively low risk was comparable to the one found in a large Dutch retrospective study, including 1000 children born to mothers with IBD, in which 3% of the thiopurine-exposed children and 2% of the non-exposed had a congenital anomaly.[32] The difference between the congenital anomaly risk reported in IBD pregnancies after in utero exposure to allopurinol and the overall risk found in our review, might be explained by the use of a different study design. In both our cohort and in most studies included in the systematic review IBD sub-analysis, all allopurinol-exposed pregnancies within a specific timeframe were reported or, as was the case in one study, were collected via a national mail audit.[33,34] This may lead to a more

representable cohort and a decreased risk of over-reporting congenital anomalies. In contrast, the studies in which allopurinol was used for a different maternal indication were mostly case reports/series or included a patient cohort that was referred to a clinical teratology and drug risk assessment clinic for risk consultation.[20] Moreover, our data suggest that a maternal allopurinol dosage of ≤100 mg/day, as prescribed in IBD pregnancies, might give a lower risk of congenital anomalies (10.3%, 6/58 cases) than a dosage of >100 mg/day (26.7%, 4/15 cases). However, due to a high percentage of missing data in relation to allopurinol dosage in pregnancy (43%, 56/129 cases), more research is necessary to determine the precise influence of maternal allopurinol dosage on the risk of congenital anomalies.

Previous reports compared maternal allopurinol use to mycophenolate use, as the two cases with a comparable pattern of congenital anomalies which occurred during maternal allopurinol exposure resembled congenital anomalies which occurred during mycophenolate usage.[20,23,35] The latter is an immunosuppressant, mostly used in transplantation medicine, which also interacts in the purine metabolism and is recognised as a teratogenic agent.[35] However, in contrast to the teratogenicity observed during mycophenolate therapy, the association between allopurinol and teratogenicity is scarce and mostly limited to the two cases with comparable major congenital anomalies with a potential uncertain causality, especially since additional genetic analysis was not performed.[20,23] Moreover, additional risk factors for congenital anomalies, as maternal behaviours and environmental exposures, paternal health or low socioeconomic status were not provided in these two cases.[20,23]

The overall risk of preterm birth was high, given that one in six children was born premature. The high risk of preterm birth persisted when excluding one case-series including 27 live born infants with a preterm birth rate of 19% in allopurinol-exposed pregnancies.[20] We cannot rule-out that there is a true association between allopurinol in utero exposure and risk of preterm birth. However, the increased risk of preterm birth in our review could potentially be influenced by maternal co-morbidity but also by the high congenital anomaly risk in the included studies, since these factors significantly impact the likelihood of being born preterm.[36] When only looking at IBD pregnancies, the risk of preterm birth was also relatively high in both the systematic review (11.8%) and our study (11.1%), but comparable to the risk reported in previous large prospective and retrospective studies. The prospective American PIANO registry including 1712 pregnant IBD patients of whom 379 were not exposed to biologicals nor thiopurines, reported preterm birth in 10% of singleton non-exposed pregnancies.[30] While the European retrospective TEDDY study (453 non-exposed pregnancies) and a Dutch retrospective cohort study (564 non-exposed pregnancies) reported a preterm birth risks of 7.3% and 11% in non-exposed IBD pregnancies, respectively.[32,37] Non-exposed pregnancies were in the TEDDY study defined as no maternal anti-TNFα use and in the Dutch study as not exposed to anti-TNFα nor thiopurines.[32,37]

The risk of SGA is highly dependent on the reference population.[38,39] The risk of SGA in our multicentre IBD study (15.2%) was increased compared to the general population in the Netherlands (9.5%), when using a comparable definition.[40] Possibly, this difference could be explained by the fact that all patients in our cohort had a chronic disease, which is a known risk factor.[41] When specifically looking at IBD pregnancies, one Dutch study including 1000 children born to mothers with IBD, reported a SGA risk of 3% and 4% in thiopurine-exposed and non-exposed children, respectively.[32] However, this study used another and older Dutch reference curve. Furthermore, they defined SGA as a weight below 2 SD for gestational age. When applying this older definition and curve in our cohort, none of the children in the present study were born SGA.[32,42]

Data about the safety of allopurinol continuation during breast-feeding are very limited. There is only one case report which demonstrated that both allopurinol and the active metabolite oxypurinol were transferred via breastmilk in a woman treated with a daily dose of 300 mg allopurinol.[43] In her exclusively breastfed infant this led to near-therapeutic dose and plasma levels without any reported adverse events.[43] In the present study, the rate of breastfeeding during allopurinol treatment was low but comparable to the results found in a Dutch study including 1000 infants born to women with IBD in which breastfeeding rates varied between 19% and 56% depending on the medical maternal treatment.[32] A Danish population-based study, including 105 women diagnosed with CD who gave birth, also demonstrated that the main reason for being non-adherent to medication was fear of transmission of medication to breastmilk.[44] This could indicate that the type of medical treatment influences the mother's choice regarding breastfeeding. Moreover, the ECCO guideline stated that due to limited data no recommendation was made regarding breastfeeding and allopurinol, which might also result in an advice from the treating physician against breastfeeding.[11]

Although being the largest study to date, it is still limited by the small sample size, so it is possible that uncommon congenital anomalies related to allopurinol use were not detected. The inclusion of multiple pregnancies from the same woman could also induce bias. We also recognise the existence of missed and therefore not reported cases, especially since in some centres the hospital database was queried while in other centres the physician identified the patients by personal recall. Moreover, since all of our patients with IBD were treated simultaneously with low-dose thiopurines and maternal 6-thioguanine nucleotide levels were only measured in four women, we cannot determine whether maternal and/or neonatal complications are related to the relatively low-dose thiopurines or to allopurinol. Our literature review was limited due to heterogeneity between the studies with different dosages of allopurinol usage, variety of co-medication and indications, as well as the lack of control groups. As a consequence, the results are difficult to compare and interpret, and a meta-analysis of studies comparing the teratogenicity could not be performed. Moreover, it is very likely that our results are affected by a publication bias.

In conclusion, due to the possibility of reporting bias, the current evidence about the teratogenicity of varying dosages of allopurinol in all types of patients remains limited and is mainly restricted to two

similar cases with major congenital anomalies. Interestingly, both the present study in IBD-pregnancies and the systematic review sub-analysis in IBD-pregnancies revealed a relatively low risk of congenital malformations after foetal exposure to a low dose of allopurinol in pregnancy. Nevertheless, larger studies are needed to draw firm conclusions about risk of adverse pregnancy outcomes such as congenital anomalies and preterm birth after allopurinol exposure in pregnancy. Further, long-term safety data in infants exposed in utero to allopurinol are warranted.

AUTHOR CONTRIBUTIONS

Femke Crouwel: Data curation; formal analysis; investigation; project administration; writing – original draft; visualization. **Melek Simsek:** Conceptualization; data curation; investigation; project administration; writing – review and editing. **Marjon A. de Boer:** Investigation; writing – review and editing. **Dirk P. van Asseldonk:** Investigation; writing – review and editing; resources. **Abha Bhalla:** Investigation; writing – review and editing; resources. **Angelique L. M. Weusthuis:** Investigation; writing – review and editing; resources. **Lennard P. L. Gilissen:** Investigation; writing – review and editing; resources. **Robert J. Verburg:** Investigation; writing – review and editing; resources. **Wout G. N. Mares:** Investigation; writing – review and editing; resources. **Bindia Jharap:** Investigation; writing – review and editing; resources. **Johan P. Kuijvenhoven:** Writing – review and editing; investigation; resources. **Bas Oldenburg:** Investigation; writing – review and editing; resources. **Hans J. C. Buiter:** Writing – review and editing. **Mette Julsgaard:** Investigation; resources; writing – review and editing. **Nanne K. de Boer:** Conceptualization; investigation; resources; supervision; writing – review and editing.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

How to cite this article: Crouwel F, Simsek M, de Boer MA, van Asseldonk DP, Bhalla A, Weusthuis ALM, et al. Multicentre study and systematic review: Allopurinol exposure during pregnancy. Aliment Pharmacol Ther. 2024;60:503–518. https://doi.org/10.1111/apt.18126