

Original Article

Safety of Tioguanine During Pregnancy in Inflammatory Bowel Disease

Sophie A. van den Berg,^a Marjon de Boer,^b Andrea E. van der Meulen-de Jong,^c Jeroen M. Jansen,^d Frank Hoentjen,^e Maurice G. V. M. Russel,^f Nofel Mahmmod,^g Adriaan A. van Bodegraven,^{a,h} C. Janneke van der Woude,ⁱ Chris J. J. Mulder,^a Nanne K. H. de Boer^a

^aDepartment of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, The Netherlands

^bDepartment of Obstetrics and Gynaecology, VU University Medical Center, Amsterdam, The Netherlands

^cDepartment of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands

^dDepartment of Gastroenterology and Hepatology, Onze Lieve Vrouwe Gasthuis Amsterdam, Amsterdam, The Netherlands

^eDepartment of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, The Netherlands

^fDepartment of Gastroenterology and Hepatology, Medical Spectrum Twente, Enschede, The Netherlands

^gDepartment of Gastroenterology and Hepatology, St Antonius Hospital, Nieuwegein, The Netherlands

^hDepartment of Internal Medicine, Geriatrics and Gastroenterology, Orbis Medical Center, Sittard-Geleen, The Netherlands

ⁱDepartment of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands

Corresponding author: Nanne K. H. de Boer, MD PhD, Department of Gastroenterology and Hepatology, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands. Tel: 0031-20-4440613; fax: 0031-20-4440554; Email: khn.deboer@vumc.nl

Abstract

Background and Aims: Conventional thiopurine [azathioprine and mercaptopurine] treatment during pregnancy in patients with inflammatory bowel disease [IBD] is considered to be safe; however data on the safety and teratogenicity of the non-conventional thiopurine tioguanine [TG] in pregnant IBD patients are lacking. We aim to describe the safety and teratogenicity of TG treatment during pregnancy in IBD patients.

Methods: This was a retrospective, multicentre descriptive case series of female IBD patients using TG during pregnancy. Data on disease and medication history, pregnancy complications, pregnancy outcome, mode of delivery, preterm birth, birthweight, congenital abnormalities, laboratory signs of myelosuppression or hepatotoxicity, and 6-thioguaninenucleotide [6-TGN] concentrations in mother and neonate were collected.

Results: In all, 13 patients [77% Crohn's disease, 23% ulcerative colitis] used TG [median dose 18g/day] during pregnancy; 19 pregnancies, including 1 twin pregnancy, were included. Spontaneous abortion occurred in three pregnancies. In 7 of the 16 ongoing pregnancies a caesarean section was performed. One neonate had a mild congenital abnormality [distal shaft hypospadias]. In the singleton pregnancies, the median birthweight was 3410g at a median of gestational age of 39 weeks. No preterm birth [< 37 weeks] or low birthweight [< 2500 g] was observed in the singleton newborns. In the twin pregnancy an induction of labour was performed at 35 + 1 weeks of gestation because of pre-eclampsia. Both neonates had a low birthweight.



Conclusions: This relatively small case series supports safe use of TG in pregnant IBD patients. Still, consideration should be given to the indication and continuation of TG during pregnancy.

Key Words: Pregnancy; tioguanine; inflammatory bowel disease

1. Introduction

Inflammatory bowel disease [IBD] has a peak prevalence during the reproductive years. An exacerbation in disease activity during conception and pregnancy is associated with low birthweight and premature birth.^{1,2,3} Consequently, it is of great importance that the safety profile of maintenance medication prescribed during pregnancy is balanced against the potential risk of disease relapse for both mother and fetus.

Conventional immune-modulating thiopurines, azathioprine [AZA] and mercaptopurine [MP], have proven to be effective in IBD in both inducing and maintaining clinical remission.^{4,5} The use of these thiopurines during pregnancy is considered relatively safe.^{6,7,8,9,10}

In contrast to MP and its precursor AZA, the metabolism of tioguanine [TG] is relatively simple, as TG is more directly converted to the pharmacologically active 6-thioguaninenucleotides [6-TGN]. Tioguanine [TG] is considered a potential rescue thiopurine which has shown to be effective in case of intolerance or resistance to conventional thiopurines.^{11,12,13,14} An unfavourable 'skewed' thiopurine metabolism, in which predominantly 6-methylmercaptopurine [6-MMP] is produced instead of the desired 6-TGN, is also considered a reason for alternative thiopurine therapy.¹⁴ Since part of the generated end metabolites of TG, being 6-TGN, is the same as during AZA and MP therapy, one could assume the same influence of TG on pregnancy outcomes.

Available data on the use of TG during pregnancy are scarce¹⁵ and consists of only two patients with Crohn's disease [CD] with no adverse pregnancy outcomes.¹⁶ Therefore, the aim of this study on female IBD patients was to describe the safety and teratogenicity of TG during pregnancy in a larger group of patients.

2. Materials and Methods

2.1. Study design

The VU University Medical Center [VUmc] IBD database was scrutinised for this retrospective study. The Initiative on Crohn and Colitis [ICC] and Nurses Initiative on Crohn and Colitis [NICC] network, being all university IBD centres in The Netherlands, were contacted as well, in search for additional cases, between 2003 and December 2014. Female IBD patients were included if they were treated with TG at some point during pregnancy. The two patients described by de Boer in 2005 were also included.¹⁶

The primary goal of this study was to describe the number and aspect of birth defects, and in addition to portray the rate of miscarriage, preterm delivery [< 37 weeks], low birthweight, and neonatal morbidity. Secondary endpoints of this study were to describe complications during pregnancy, method of delivery, course after delivery, signs of myelosuppression or hepatotoxicity in the neonate, thiopurine metabolite measurements, and follow-up. Ethics approval was obtained from the medical ethics board of VU University Medical Center.

2.2. Demographic and IBD-related characteristics

At baseline, the following data on patient characteristics were collected: type of IBD [CD, ulcerative colitis [UC], or IBD unclassified], localisation of IBD, duration of IBD at initiation of TG treatment and conception, medication history, and co-medication. Data on duration between diagnosis, TG treatment, and conception were collected in whole years. Patients were classified according to the Montreal classification.¹⁷

2.3. Pregnancy outcome and neonatal characteristics

The following data were collected on obstetric history, pregnancy, and neonatal outcome: previous pregnancies and outcome, spontaneous abortions, course of pregnancy, flare of disease activity during pregnancy and treatment, fetal ultrasound abnormalities, mode of delivery, indications for operative delivery, gender, birthweight, gestational age at birth, congenital abnormalities, neonatal complications, and neonatal ward admission. Birthweight percentile categories were calculated according to gender and gestational age at birth.¹⁸

2.4. Laboratory tests

If measured, thiopurine metabolite 6-TGN concentrations in red blood cells [RBCs] were determined using the Dervieux method.¹⁹ Existing literature generally utilises the Lennard method²⁰ for determination of thiopurine metabolites. To compare our data, 6-TGN concentrations were re-calculated by dividing the concentrations by a converting factor of 2.6.²¹

In blood, both cord blood and neonatal venepuncture, potential toxicity [bone marrow depression and hepatotoxicity] due to maternal thiopurine use was analysed. In newborns, leukopenia was defined as a leucocyte count below $5 \times 10^9/l$, anaemia as a haemoglobin level below 10 mmol/l and thrombocytopenia as a platelet count below $150 \times 10^9/l$.²² Hepatotoxicity was defined as either alanine aminotransferase [ALT] > 50 U/l, aspartate aminotransferase [AST] > 140 U/l, alkaline phosphatase [AP] > 300 U/l, or gamma glutamyltransferase [GGT] > 263 U/l.²³ Hypoglycaemia was defined as blood glucose level below 3.0 mmol/l. Neonatal hyperbilirubinaemia was defined as bilirubin level at Day 1 above 100 $\mu\text{mol/l}$.²³

2.5. Data analysis

Demographic data are given descriptively and tabulated. Separate cases are noted as #[patient]/no.[neonate]. Data are expressed as median with interquartile range [IQR] according to distribution. Median birthweight and median gestational age at birth are determined for the singleton pregnancies. No further statistical analysis was performed, as the group of patients was too small for proper analysis. Outcomes were compared with data from a recent Dutch prospective cohort study on the use of conventional thiopurines in pregnant IBD patients.⁷

3. Results

3.1. Maternal characteristics

A total of 13 female patients were included with a median age at diagnosis of 20 years old [IQR 17–22] from six hospitals. Crohn's disease and UC were diagnosed in 10 [78%] and 3 [23%] patients, respectively. Maternal characteristics are provided in Table 1.

Reasons for initiation of TG treatment include a combination of the following: corticosteroid dependency [N = 3], failure and/or intolerance of corticosteroid therapy [N = 3], failure and/or intolerance using conventional thiopurines [N = 11], failure and/or intolerance on 5-aminosalicylic acid [5-ASA] treatment [N = 3], loss of response and/or intolerance of anti-tumour necrosis factor- α [anti-TNF- α] [mono]therapy [N = 4], negative effects of methotrexate [N = 2], or a 'skewed' thiopurine metabolism [N = 2].

Median duration of diagnosis to initiation of TG treatment was 9 years [IQR 4–11]. Median dose of TG during pregnancy was 18 g/day [IQR 18–21]; three patients were dosed three times a week instead of daily administration. All patients received TG throughout the entire pregnancy, except for one [case #12/1] in whom TG therapy was terminated at 30 weeks of gestation. Co-medication was received in six patients, (anti-TNF- α [N = 2], 5-ASA [N = 2], and corticosteroids [N = 4]).

3.2. Pregnancy characteristics

All 13 patients using TG during pregnancy, with a total of 19 pregnancies including one monochorionic twin pregnancy were included [Table 2]. In line with good clinical practice, patients received a pre-counselling talk on the safety of TG treatment during pregnancy, using the scarce data.¹⁵ Median age at conception was 33 years [IQR 27–36]. Median duration of initiation of TG treatment to conception was 2 years [IQR 12.5], median duration of diagnosis to conception was 11 years [IQR 8–13]. Three patients became pregnant by in-vitro fertilization [IVF], including one patient [case #5] with polycystic ovary syndrome [PCOS] who had a spontaneous abortion in her first pregnancy and in her third pregnancy; after IVF, she carried the monochorionic twins mentioned above.

3.3. Maternal complications during pregnancy

Two pregnancies [#1/1 and #5/2] were complicated by [mild] pregnancy-induced hypertension [PIH] for which no medical treatment was necessary. The twin pregnancy [#5/3 and #5/4] and one other pregnancy [#10/2] were complicated by pre-eclampsia. In three patients [#3, #8, and #10] a flare in IBD disease activity was treated with an induction tapering scheme of glucocorticoids. Other than in the three patients experiencing a flare, no IBD-related laboratory changes were observed during pregnancy.

3.4. Pregnancy outcomes

Three pregnancies resulted in a spontaneous abortion [16%] in the first trimester during TG treatment. All three patients had an ongoing pregnancy in the years following the miscarriage during TG therapy.

In 7 of the 16 ongoing pregnancies, delivery was by caesarean section. Four elective caesarean sections were performed, indicated by perianal disease [N = 3] and breech position of the fetus [N = 1]. Three emergency caesareans were performed because of obstructed labour in two, and for suspected fetal distress in the twin pregnancy. In this monochorionic twin pregnancy, labour was induced at 35 + 1 weeks of gestation because of pre-eclampsia [cases #5/3 and #5/4]. Due to suspected fetal distress during induction, an emergency caesarean was performed. In total, 17 neonates were born. Of the 15 singleton newborns, median gestational age at birth was 39 weeks [IQR 38–40] and median birthweight was 3410 g [IQR 3267–3815]. The twins were born with birthweights of 2470 g and 2160 g, respectively.

3.5. Neonatal complications

Admission to the neonatology unit was indicated in five newborns, of whom the characteristics are described in Table 3. The monochorionic twins were both admitted to the neonatology unit because of infant respiratory distress syndrome [IRDS] grade 2, treated with continuous positive airway pressure [CPAP], and postpartum transient hypotonia due to maternal labetalol use for pre-eclampsia.

Table 1. Patient characteristics. Values are number or median (interquartile range [IQR]).

Patient characteristics [mothers] [N = 13]	Jharap [2014] [N = 30] ⁷			
Age at diagnosis [years]	20	[17–22]	21	
CD/UC	10/3		24/6	
Montreal classification of UC patients				
▪ E2	1		3	
▪ E3	2		3	
Montreal classification of CD patients				
▪ A1/A2/A3	1/9/0		7/17/0	
▪ L1/L2/L3	2/3/5		7/7/10	
▪ B1/B2/B3/B1p/B2p/B3p/missing	5/3/1/0/0/1/0		11/4/0/7/1/0/1	
Parity [≥ 1]	7		-	
No. of patients with previous spontaneous abortion	2		-	
No. of patients with previous IBD surgery	3		-	
Age at conception [years]	33	[27–36]	30	[27–33]
Duration IBD to conception	11	[8–13]	8.5	[6–12]
Dose of TG [mg/day]	18	[18–21]	-	
Co-medication				
▪ Anti-TNF- α	2		3	
▪ 5-ASA	2		6	
▪ Corticosteroids	4		2	

IBD, inflammatory bowel disease; 5-ASA, 5-aminosalicylic acid; CD, Crohn's disease; TG, tioguanine; anti-TNF- α , anti-tumour necrosis factor- α ; UC, ulcerative colitis.

In one pregnancy [case #12/1] the fetus was in a breech presentation. After birth by elective caesarean section, the neonate was admitted to the neonatology unit because of transient tachypnoea of the newborn [TTN] which indicated CPAP therapy. Also, a sacral dimple was found on physical examination, but ultrasonography showed no neural tube defect.

Two neonates [12%] were large for gestational age [LGA: birthweight percentile > 97.7]. Of these one [case #1/1] was admitted to the neonatal ward because of hypoglycaemia, which normalised after glucose infusions, and premature atrial contractions [PACs] which spontaneously resolved. In this neonate, a distal shaft hypospadias was diagnosed by the paediatric urologist.

One neonate [case #5/2] was briefly admitted to the neonatal ward for glucose control and an adrenocorticotrophic hormone [ACTH] test because of maternal prednisone use, with no adverse outcomes.

3.6. Laboratory testing

Five neonates were laboratory tested for myelosuppression in either cord blood or by neonatal thrombocytopenia. No anaemia, leukopenia, or thrombocytopenia was observed. No hepatotoxicity was found in the three neonates checked. No clinically relevant maternal liver test abnormalities were observed during pregnancy. Hypoglycaemia was detected in 60% of the five newborns tested.

Table 2. Pregnancy characteristics. Values are absolute number [percentage].

Pregnancy characteristics [N = 19]		
Spontaneous abortion	3 ^a	[16%]
Complicated pregnancy	6	
▪ Flare IBD	3	
▪ Pregnancy-induced hypertension	2	
▪ Pre-eclampsia	2	
Mode of delivery	16	
▪ Elective caesarean section	4	
▪ Emergency caesarean section	3 ^b	
▪ Vaginal delivery	9	

IBD, inflammatory bowel disease.

^aOne spontaneous abortion after in-vitro fertilisation in a patient with polycystic ovary syndrome. ^bIncluding one twin pregnancy.

Table 3. Neonatal characteristics. Values are number [percentage] or median (interquartile range [IQR]).

Neonatal characteristics [N = 17]		Jharap [2014] [N = 31] ⁷	
Congenital anomalies	1 ^a [6%]	2 ^b [6.5%]	
Gestational age at birth [weeks]	39 [38–40]	39 [38–40.1]	
▪ Preterm birth [< 37 wk GA]	2 ^c [12%]	3 ^c [10%]	
▪ Post-term birth [> 42 wk GA]	0 [0%]	0 [0%]	
Birthweight [g]	3410 [3267–3815]	3410 [3200–3680]	
▪ LBW [1500–2500 g]	2 ^c [12%]	3 ^c [10%]	
▪ SGA [<i>p</i> < 10]	0 [0%]	-	
▪ LGA [<i>p</i> > 97.7]	2 [12%]	-	
Neonatal ward admission	5 ^c [29%]	-	
Anaemia	0/5 [0%]	10 [63%]	

GA, gestational age; wk, weeks; LBW, low birthweight; LGA, large for gestational age; SGA, small for gestational age.

^aDistal shaft hypospadias in patient #1/1 whose father also has a congenital hypospadias.

^bClubfoot and isolated ptosis of left eye.

^cIncluding the twins.

Umbilical cord 6-TGN concentrations were measured in four newborns. In three, the 6-TGN concentration was below detectable level; in one newborn, the re-calculated concentration was 38 pmol/8*10⁸ RBC.¹⁶

3.7. Comparison pregnancy cohort using conventional thiopurines

The population from a recent prospective cohort study in The Netherlands, on maternal conventional thiopurine therapy during pregnancy,⁷ closely resembles our TG cohort as based on the patient and disease characteristics [Table 1]. In addition, neonatal outcomes match with our rate of congenital abnormalities, birthweight, and gestational age at birth [Table 4].

4. Discussion

Our descriptive study demonstrates that TG treatment in pregnant IBD patients appears to be relatively safe: 19 pregnancies in 13 patients resulted in 17 neonates, including one with a mild congenital abnormality. Five newborns required [short-term] neonatal ward admission, including the twins after induced preterm labour. Low birthweight [< 2500 g] was only observed in these twins, and in none of the singletons.

Conventional thiopurine treatment during pregnancy in IBD patients is considered relatively safe. There is no association with an increase in the rate of congenital abnormalities or low birthweight when adjusted for disease activity, though it may increase the risk of preterm birth,⁶ neonatal anaemia, and leukopenia.⁷ Also, maternal thiopurine treatment during pregnancy does not seem to affect the long-term development or immune function of children up to 6 years of age.¹⁰ As the metabolites of TG are partially the same as the metabolites of AZA and MP, a comparable impact of TG on pregnancy outcomes could be expected.

Therefore we compared our patient data and outcomes with a Dutch age-matched IBD cohort of 30 women taking conventional thiopurines during pregnancy.⁷ As shown in Tables 1 and 4, not only the patient group but also the pregnancy outcomes, i.e. birthweight and rate of congenital abnormalities, are highly similar.

In our study, the observed birthweight was comparable to the normal ranges within the data from the 10-year prospective perinatal registration in The Netherlands.²⁴ Low birthweight [LBW], specified as birthweight below 2500g, occurred in our study only

Table 4. Details of neonatal complications. Cases are noted # [patient]/no. [neonate]. Presented patients had no previous IBD surgery.

Complication	#1/1	#5/2	#5/3 ^a	#5/4 ^a	#12/1
Maternal disease	UC	CD			UC
Maternal TG dose [mg/day]	18	18	18		21
Co-medication	Anti-TNF α	Anti-TNF α , 5-ASA, corticosteroids	Anti-TNF α , 5-ASA, corticosteroids, ketanserin, labetalol		No
Complication of pregnancy	Pregnancy-induced hypertension	Pregnancy-induced hypertension	Pre-eclampsia		No
Mode of delivery	ECS for prolonged labour	Vaginal delivery	ECS for fetal distress		PCS for breech position
Gestational age at birth [weeks + days]	40 + 1	39 + 2	35 + 1		39 + 1
Birthweight [g]	4445	3400	2470	2160	3410
Birthweight percentile	>9 7.7	P5080	P2050	P1620	P2050
Apgar score	9/10/10	9/10/10	5/7/8	3/7/8	7/7
Congenital anomalies	Distal shaft hypospadias	No	No	No	No
Indications for neonatal ward admission	<ul style="list-style-type: none"> LGA with hypoglycaemia, paroxysmal atrial contractions, spontaneously resolved 	<ul style="list-style-type: none"> Glucose control and ACTH test because of maternal prednisone use 	<ul style="list-style-type: none"> IRDS grade 2 treated with CPAP, hyperbilirubinaemia of 171 $\mu\text{mol/l}$, hypotonia directly postpartum due to maternal labetalol use 	<ul style="list-style-type: none"> IRDS grade 2 treated with CPAP, hyperbilirubinaemia of 171 $\mu\text{mol/l}$, hypotonia directly postpartum due to maternal labetalol use 	<ul style="list-style-type: none"> Wet lung treated with CPAP, ultrasonography of sacral dimple showing no neural tube defect
Placental abnormalities	No	No	Monochorionic-diamniotic placenta with vascular anastomoses		No

IBD, inflammatory bowel disease; 5-ASA 5-aminosalicylic acid, ACTH adrenocorticotropic hormone, CD Crohn's disease, CPAP continuous positive airway pressure, ECS emergency caesarean section, IRDS infant respiratory distress syndrome, PCS primary caesarean section, TG tioguanine, anti-TNF- α anti-tumour necrosis factor- α , LGA large for gestational age, UC ulcerative colitis.

^aTwin pregnancy.

in the twin pregnancy. No intrauterine growth restriction defined as birthweight percentile [$p < 10$], was observed.

A meta-analysis on the influence of IBD on pregnancy shows an increased rate of LBW in IBD patients compared with a non-IBD population.³ In the general Dutch population, the rate of LBW is 6.9%.²⁴ In our cohort, no LBW was observed in the singleton pregnancies, whereas a French study on pregnancy outcome in IBD patients treated with conventional thiopurines shows a LBW rate of 15.8%.⁸

Inflammatory bowel disease also influences the rate of prematurity [< 37 weeks of gestation] compared with controls.³ In conventional maternal thiopurine treatment, rates up to 36.2% of preterm birth are reported,^{8,9} compared with 7.7% as documented by the perinatal registration in The Netherlands.²⁴ No preterm birth in singleton pregnancies was observed in our case series. Only the twin pregnancy resulted in an iatrogenic preterm birth.

One congenital abnormality was diagnosed, namely a distal shaft hypospadias in a neonate whose father also had congenital hypospadias. The prevalence of congenital hypospadias in The Netherlands is 19.8 per 10,000 births.²⁴ Studies on maternal thiopurine treatment in IBD report rates of 3.6–6.5%^{7,8,9} of congenital abnormalities, whereas the rate of congenital abnormalities in the general population in The Netherlands is 2.7%.²⁶ However, next to an increased rate of low birthweight and prematurity, the meta-analysis on the influence of IBD on pregnancy also shows a 2.37-fold increased risk of congenital abnormalities compared with a non-IBD population.³ Moreover, hypospadias shows familial clustering,²⁷ and environmental factors including maternal drug use during pregnancy are also contributing factors.²⁸ Therefore, we cannot determine whether the congenital hypospadias in this case is a consequence of IBD disease activity or maternal therapy, or has a familial cause.

Three pregnancies [16%] ended in a spontaneous abortion in the first trimester. Several maternal risk factors were present, including maternal age above 35 years, previous spontaneous abortions, comorbid PCOS and conception by IVF.²⁹ Since our cohort is relatively small, we believe no firm conclusions can be drawn from this rate.

In five newborns, a blood sample was drawn for analysis of potential toxicity [hepatotoxicity and myelosuppression] of maternal thiopurine therapy. No anaemia was present, although another study observed a rate of 60% [in 31 newborns] of anaemia after intrauterine exposure to conventional thiopurines.⁷

We acknowledge several limitations in this retrospective study. Because of the design of the study, disease activity at conception and during pregnancy was not documented. Data on smoking and alcohol intake during pregnancy were not available in the outpatient gastroenterology medical reports. Dosage of medication was not recalculated to mg/kg since data on maternal weight were not retrospectively obtainable. We recognise the probable existence of missed and therefore unreported cases. Also, precise numbers on voluntarily childlessness using TG treatment are missing, though this finding is mentioned by several gastroenterologists contributing to this article. Despite the multicentre design, the sample size was relatively small; however, our study represents the largest case series so far in literature. In the majority of neonates no [long-] follow-up was performed.

Our study reveals a lower incidence of adverse pregnancy outcomes compared with the general Dutch population, though unfavourable effects of IBD disease activity itself were expected.³ Low birthweight and preterm birth were not observed in the singleton pregnancies. This is a reassuring outcome, especially when compared

with general data on IBD disease activity during pregnancy³ and evidence on conventional maternal thiopurine therapy during pregnancy,^{6,7} which show increased rates of both LBW and preterm birth. Only the twin pregnancy resulted in neonates with LBW after a preterm delivery, which is an average pregnancy outcome for twins. Also, the one [mild] congenital abnormality in this cohort has multifactorial potential causes.^{3,27,28}

In conclusion, this relatively small case series shows promising outcomes and supports safe use of TG in pregnant IBD patients. Although there is no evident proof of teratogenicity, consideration should be given to the indication and continuation of TG during pregnancy, and dedicated specialist teams are recommended for pregnancy management.

Funding

None received.

Conflict of Interest

None.

Acknowledgments

Guarantor of the article: NB. Author contributions: SB, NB, study concept, design, drafting of the manuscript, and descriptive analysis; SB, AM, JJ, FH, MR, NM, AB, CW, acquisition of data and revision of the manuscript; MB, analysis, interpretation of data and critical revision of the manuscript; CM, study supervision. All authors read and approved the final manuscript, including the authorship list.

References

- Bush MC, Patel S, Lapinski RH, *et al.* Perinatal outcomes in inflammatory bowel disease. *J Matern Fetal Neonatal Med* 2004;15:237–41.
- Reddy D, Murphy SJ, Kane SV, *et al.* Relapses of inflammatory bowel disease during pregnancy: in-hospital management and birth outcomes. *Am J Gastroenterol* 2008;103:1203–9.
- Cornish J, Tan E, Teare J, *et al.* A meta-analysis on the influence of inflammatory bowel disease on pregnancy. *Gut* 2007;56:830–7.
- Chande N, Tsoulis DJ, MacDonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2013;4:CD000545.
- Timmer A, McDonald JW, MacDonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2007;1:CD000478.
- Akbari M, Shah S, Velayos FS, *et al.* Systematic review and meta-analysis on the effects of thiopurines on birth outcomes from female and male patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013;19:15–22.
- Jharap B, de Boer NK, Stokkers P, *et al.* Intrauterine exposure and pharmacology of conventional thiopurine therapy in pregnant patients with inflammatory bowel disease. *Gut* 2014;63:451–7.
- Coelho J, Beaugerie L, Colombel JF, *et al.* Pregnancy outcome in patients with inflammatory bowel disease treated with thiopurines: cohort from the CESAME Study. *Gut* 2011;60:198–203.
- Shim L, Eslick GD, Simring AA, *et al.* The effects of azathioprine on birth outcomes in women with inflammatory bowel disease [IBD]. *J Crohns Colitis* 2011;5:234–8.
- de Meij TG, Jharap B, Kneepkens CM, *et al.* Long-term follow-up of children exposed intrauterine to maternal thiopurine therapy during pregnancy in females with inflammatory bowel disease. *Aliment Pharmacol Ther* 2013;38:38–43.
- Derijks LJ, de Jong DJ, Gilissen LP, *et al.* 6-Thioguanine seems promising in azathioprine- or 6-mercaptopurine-intolerant inflammatory bowel dis-

- ease patients: a short-term safety assessment. *Eur J Gastroenterol Hepatol* 2003;15:63–7.
12. de Boer NK, Reinisch W, Teml A, *et al.* 6-Thioguanine treatment in inflammatory bowel disease: a critical appraisal by a European 6-TG working party. *Digestion* 2006;73:25–31.
 13. Dubinsky MC, Feldman EJ, Abreu MT, *et al.* Thioguanine: a potential alternate thiopurine for IBD patients allergic to 6-mercaptopurine or azathioprine. *Am J Gastroenterol* 2003;98:1058–63.
 14. Bonaz B, Boitard J, Marteau P, *et al.* Thioguanine in patients with Crohn's disease intolerant or resistant to azathioprine/mercaptopurine. *Aliment Pharmacol Ther* 2003;18:401–8.
 15. van der Woude CJ, Ardizzone S, Bengtson MB, *et al.* ECCO Guidelines/Consensus Paper: The Second European Evidenced-based Consensus on Reproduction and Pregnancy in Inflammatory Bowel Disease. *J Crohns Colitis* 2015;9:107–24.
 16. de Boer NK, van Elburg RM, Wilhelm AJ, *et al.* 6-Thioguanine for Crohn's disease during pregnancy: thiopurine metabolite measurements in both mother and child. *Scand J Gastroenterol* 2005;40:1374–7.
 17. Satsangi J, Silverberg MS, Vermeire S, *et al.* The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006;55:749–53.
 18. Visser GH, Eilers PH, Elferink-Stinkens PM, *et al.* New Dutch reference curves for birthweight by gestational age. *Early Hum Dev* 2009;85:737–44.
 19. Dervieux T, Bouliou R. Simultaneous determination of 6-thioguanine and methyl 6-mercaptopurine nucleotides of azathioprine in red blood cells by HPLC. *Clin Chem* 1998;44:551–5.
 20. Lennard L. Assay of 6-thioinosinic acid and 6-thioguanine nucleotides, active metabolites of 6-mercaptopurine, in human red blood cells. *J Chromatogr* 1987;423:169–78.
 21. Shipkova M, Armstrong VW, Wieland E, *et al.* Differences in nucleotide hydrolysis contribute to the differences between erythrocyte 6-thioguanine nucleotide concentrations determined by two widely used methods. *Clin Chem* 2003;49:260–8.
 22. Pekelharing JM, Souverijn JHM, Hooijkaas H. *Handboek medische laboratoriumdiagnostiek [Handbook of Medical Laboratory Diagnostics]*. Houten, The Netherlands: Prelum, 2009.
 23. Rosenthal P. Assessing liver function and hyperbilirubinemia in the newborn. National Academy of Clinical Biochemistry. *Clin Chem* 1997;43:228–34.
 24. Foundation Perinatal Registration. *Ten Years of Perinatal Registration in The Netherlands*. Utrecht, The Netherlands: Foundation Perinatal Registration The Netherlands, 2011.
 25. Rijks University Groningen. *Prevalence of Congenital Anomalies: Time Trends 2003–2012*. <http://www.rug.nl/research/genetics/eurocat/pdf/timetrends-2014.pdf> Accessed October 31, 2014.
 26. Rijks University Groningen. *General Figures*. <http://www.rug.nl/research/genetics/eurocat/pdf/general-figures-2014.pdf> Accessed October 31, 2014.
 27. Fredell L, Iselius L, Collins A, *et al.* Complex segregation analysis of hypospadias. *Hum Genet* 2002;111:231–4.
 28. van der Zanden LF, van Rooij IA, Feitz WF, *et al.* Aetiology of hypospadias: a systematic review of genes and environment. *Hum Reprod Update* 2012;18:260–83.
 29. Nybo Andersen AM, Wohlfahrt J, Christens P, *et al.* Maternal age and fetal loss: population based register linkage study. *BMJ* 2000;320:1708–12.