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Original Article

Exposure to Thioguanine During 117 Pregnancies in Women With Inflammatory Bowel Disease

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Abstract

Background: Safety of thioguanine in pregnant patients with inflammatory bowel disease [IBD] is sparsely recorded. This study was aimed to document the safety of thioguanine during pregnancy and birth.

Methods: In this multicentre case series, IBD patients treated with thioguanine during pregnancy were included. Data regarding disease and medication history, pregnancy course, obstetric complications, and neonatal outcomes were collected.

Results: Data on 117 thioguanine-exposed pregnancies in 99 women were collected. Most [78%] had Crohn's disease and the mean age at delivery was 31 years. In 18 pregnancies [15%], IBD flared. Obstetric and infectious complications were seen in 15% [$n = 17$] and 7% [$n = 8$] of pregnancies, respectively. Ten pregnancies [8.5%] resulted in a first trimester miscarriage, one in a stillbirth at 22 weeks of gestational age

and one in an induced abortion due to trisomy 21. In total, 109 neonates were born from 101 singleton pregnancies and four twin pregnancies. One child was born with a congenital abnormality [cleft palate]. In the singleton pregnancies, 10 children were born prematurely and 10 were born small for gestational age. Screening for myelosuppresion was performed in 16 neonates [14.7%]; two had anaemia in umbilical cord blood. All outcomes were comparable to either the general Dutch population or to data from three Dutch cohort studies on the use of conventional thiopurines in pregnant IBD patients.

Conclusion: In this large case series, the use of thioguanine during pregnancy is not associated in excess with adverse maternal or neonatal outcomes.

Key Words: Inflammatory bowel disease; pregnancy; thioguanine

1. Introduction

Inflammatory bowel disease [IBD] often affects young adults during their reproductive years. Maintaining remission during conception and pregnancy is crucial, considering that active disease is associated with an increased risk of worse perinatal outcomes.[1,2] Consequently, it is important that both maternal and fetal safety of maintenance therapy during pregnancy is balanced with the potential risk of disease relapse.

Exposure to azathioprine [AZA] or mercaptopurine [MP] during conception and pregnancy is considered sufficiently safe for responsible continuation during pregnancy, and its use has not been associated with a higher risk of preterm birth or low birthweight.[3] In a recent European consensus guideline, it is therefore recommended to continue thiopurine therapy during pregnancy.[4]

Thioguanine [TG] is another thiopurine derivative that has recently been licensed in The Netherlands for use in IBD after failure of conventional thiopurines. As a result it has been increasingly prescribed. In contrast to AZA and MP, TG is converted in fewer enzymatic steps to the pharmacologically active 6-thioguanine nucleotides [6-TGN].[5] Since the effector metabolites are similar for all thiopurines but less additional metabolites are formed during the conversion of TG, it could be just as safe for pregnancy, although data are scarce. Our group published one report showing no adverse pregnancy outcomes in two patients with Crohn's disease treated with TG, and in another small case series [$n = 19$] TG appeared responsibly safe for both mother and fetus.[6,7] Due to limited data on TG in pregnancy, it remains uncertain how to advise patients what to do regarding continuation of TG during the [intended] conception period and pregnancy. We therefore evaluated the teratogenicity and safety of TG during pregnancy in a large group of female IBD patients.

2. Materials and Methods

2.1. Study design

This multicentre case series was performed from December 2014 till March 2022 in 24 centres in The Netherlands. Patients were identified by their treating physician and included if they were diagnosed with Crohn's disease [CD], ulcerative colitis [UC], or IBD-unclassified [IBD-U] according to clinical, endoscopic, and/or histological criteria and if they were exposed to TG during their pregnancy. Co-medication, such as biologics, was allowed. Thioguanine exposure was defined as use of TG at any time during estimated conception and/or pregnancy. In some cases, the researchers were notified by the treating physician when patients became pregnant and data were collected prospectively; in other patients, the researchers were notified after the delivery and data were collected retrospectively. Five patients described by van den Berg in 2016 were also included.[6]

The primary aim of this study was to describe the number and characteristics of birth defects, the rate of preterm delivery (<37 weeks gestational age [GA]), and small for GA ([SGA] [<10th percentile]).[8] Secondary endpoints were the rate and type of other obstetric complications (ie, pregnancy-induced hypertension [PIH], pre-eclampsia including 'haemolysis, elevated liver enzyme levels, and low platelet levels' [HELLP],[9] intrahepatic cholestasis of pregnancy [ICP], placental abruption, hyperemesis gravidarum, gestational diabetes), infectious complications during pregnancy, the mode of delivery, and neonatal myelotoxicity.

2. 2. Maternal and IBD-related characteristics

The following patient characteristics were collected by the treating physician: age at delivery, intoxications [ie, smoking, alcohol, or drug use during conception or pregnancy], type of IBD, dosage of TG, disease duration and duration of TG use at conception, prior surgeries, obstetric history, and co-medication. Disease was classified according to the Montreal classification.[10] Data on duration between diagnosis, TG treatment, and conception were calculated in rounded years.

2.3. Pregnancy and neonatal characteristics

The following data on pregnancy and neonatal outcome were collected: method of conception including the need for assisted reproduction, disease activity during pregnancy, antibiotic-treated infections during pregnancy, obstetric complications, mode of delivery, gender, birthweight, gestational age at birth, Apgar score [1 and 5 min], congenital abnormalities, and neonatal complications.

Assisted reproduction was defined as any of the following procedures that resulted in a pregnancy: ovarian stimulation, *in vitro* fertilization [IVF], intracytoplasmic sperm injection [ICSI], or intrauterine insemination [IUI]. A loss of pregnancy before the 16th week was considered a miscarriage and after 16 weeks a stillbirth or immature delivery.[11]

Prematurity was defined as birth before 37 weeks. Small for gestational age [SGA] was defined as birthweight below the 10th percentile of the gestational age computed in the national pregnancy cohort, and large for gestational age was defined as above the 90th percentile.[8]

If measured, 6-TGN concentrations in red blood cells during pregnancy and in umbilical cord blood were mostly determined with the method of Dervieux.[12] To compare our data with existing literature, in which the method developed by Lennard and Singleton was generally used to determine metabolite levels, 6-TGN concentrations measured with the Dervieux method were divided by 1.4.[13,14]

Anaemia in newborns was defined according to the reference ranges proposed by Jopling *et al*., which account for gestational age; leukopenia was defined as a leukocyte count below 5×10^9/l and thrombocytopenia as a platelet count below 150×10^9/l.[15,16] None of the newborns was tested for hepatotoxicity. Outcomes were compared with the general Dutch population and with data from three Dutch cohort studies on the use of conventional thiopurines in pregnant IBD patients.[15,17–19]

Table 1. Maternal characteristics of all pregnancies [*n* = 117].

Maternal characteristics	*N* = 117
Age at delivery in years, mean [SD]	31 [4.2]
Disease duration in years, median [IQR]	6 [4–10]
Inflammatory bowel disease subtype, *n* [% of cases]:	
- Ulcerative colitis	23 [19.7%]
- Crohn's disease	91 [77.8%]
- IBD undetermined	3 [2.6%]
Montreal classification UC, *n* [% of cases]:	
E: extension of colitis:	
- E1 proctitis	2 [8.7%]
- E2 left-sided colitis	11 [47.8%]
- E3 extensive colitis	9 [39.1%]
- Missing	1 [4.4%]
Montreal classification CD, *n* [% of cases]:	
A: age at diagnose	
- A1 [≤16 years]	9 [9.9%]
- A2 [17–40 year]	82 [90.1%]
- A3 [≥40 years]	0 [0%]
L: disease location	
- L1: only terminal ileum	31 [34.1%]
- L2: only colon	23 [25.3%]
- L3: ileum and colon	34 [37.4%]
- +L4: locations proximal to ileum	4 [4.4%]
- +P: perianal disease	20 [22.0%]
- Missing	3 [3.3%]
B: behaviour:	
- B1: non-stricturing, non-penetrating	69 [75.8%]
- B2: stricturing	11 [12.1%]
- B3: penetrating	9 [9.9%]
- Missing	2 [2.2%]
Previous IBD surgery, *n* [% of cases]	15 [12.8%]
Smoking status, *n* [% of cases]	
- Current	6 [5.1%]
- Former [before pregnancy]	4 [3.4%]
- Never	99 [84.6%]
- Missing	8 [6.8%]
Gravidity [>1], *n* [% of cases]	50 [42.7%]
Previous miscarriage, *n* [% of cases]	11 [22.0%]
Assisted reproduction, *n* [% of cases]	17 [15%]
- ICSI	3 [2.6%]
- IVF	7 [6.0%]
- IUI	6 [5.1%]
- Ovarian stimulation	1 [0.9%]
Thioguanine dosage, mg, median [IQR]	20 [10-20]
Thioguanine used during trimester, *n* [% of cases]	
- Trimester 1	107 [91.5%]
- Trimester 2	98 [83.8%]
- Trimester 3	103 [88.0%]
- Trimesters 1–3	94 [80.3%]
IBD co-medication at conception, *n* [% of cases]	43 [36.8%]
- Mesalazine	22 [18.8%]
- Anti-TNF-α	21 [17.9%]
- Glucocorticoids	5 [4.2%]
- Vedolizumab	1 [0.9%]
- Ustekinumab	1 [0.9%]
- Other	9 [7.7%]

SD, standard deviation; IQR, interquartile range; IBD, inflammatory bowel disease; UC, ulcerative colitis, CD, Crohn's disease; IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; TNF, tumour necrosis factor.

2.4. Statistical considerations

Categorical variables were described as numbers with percentages. Continuous variables were presented as means with standard deviation [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. SPSS version 26 was used for statistical analysis.

2.5. Ethical statement

The research medical ethics committee [REC] of the VU University Medical Centre approved this study with file number 2014.530 and waived the need for written informed consent.

3. Results

3.1. Maternal characteristics

Data on 117 pregnancies in 99 women were collected. Most women were diagnosed with Crohn's disease [78%] and 67 [57%] were primigravid. The mean age at delivery was 31 years [SD 4.2]. In total, 109 neonates were born from 101 singleton pregnancies and four twin pregnancies. TG was used throughout all three trimesters in 80% with a median daily dose of 20 mg [IQR 10–20 mg]. In the other patients TG was stopped for the following reasons: patient preference [*n* = 3], start of biologics [*n* = 2], side effects [*n* = 1], breastfeeding wish [*n* = 1], and unknown [*n* = 1]. One patient ceased therapy on pharmacist advice at 10 weeks, but restarted 3 months later due to disease activity. Two patients started with TG after conception, due to either skewed metabolism with conventional thiopurines [*n* = 1] or the necessity of co-medication with allopurinol [*n* = 1]. Twelve patients did not use TG during all three trimesters due to a miscarriage, spontaneous abortion or still birth; 43 patients [37%] used co-medication at the start of pregnancy. Additional maternal characteristics are provided in Table 1.

3.2. Pregnancy complications

One or more other obstetric complications were observed in 17 pregnancies [15%] [Table 2]. Eight patients [7%] developed infectious complications during their pregnancy which required antibiotics, no one had to be hospitalised. Additional details are provided in Table 2. In one pregnancy, the mother developed postpartum fever of unknown origin, for which she was admitted for 3 days. No other infectious complications during labour or postpartum were reported. In 18 pregnancies [15%], there was a flare in IBD disease activity of varying severity, which was treated with budesonide [*n* = 7], prednisone [*n* = 5], anti-tumour necrosis factor [TNF]-α [*n* = 2], topical therapy [*n* = 5], and/or by restarting TG [*n* = 1] 3 months after discontinuation. In two pregnancies, the flare did not lead to

Table 2. Obstetric outcomes.

	Singleton pregnancies [*n* = 113]	Twin pregnancies [*n* = 4]	All pregnancies [*n* = 117]
Number of live-born children	101	8	109
Birthweight in g, median [IQR]	3355 [2965–3726]	2470 [2400–2510]	3294 [2810–3696]
Gestational age in weeks, median [IQR]	39 [38–40]	36.71 [35.43–37.14]	39 [37.9–40]
Preterm birth, *n* [% of cases]	10 [10.2, *n* = 98]]	6 [75]	16 [15.1, *n* = 106]
Small for gestational age, *n* [% of cases]	10 [10.5, *n* = 95]]	3 [37.5]	13 [12.6, *n* = 103]
Large for gestational age, *n* [% of cases]	9 [9.5, *n* = 95]	0 [0]	9 [8.7, *n* = 103]
Congenital abnormalities in live-born children, *n* [% of cases]	1 [1]	0 [0]	1 [0.9]
APGAR score < 7 after 5 min, *n* [% of cases]	5 [6, *n* = 84]	1 [12.5]	6 [6.5, *n* = 92]
Partial placental abruption, *n* [% of cases]	1 [0.9]	0 [0]	1 [0.85]
PIH, *n* [% of cases]	3 [2.7]	1 [12.5]	4 [3.4]
Gestational diabetes, *n* [% of cases]	6 [5.3]	0 [0]	6 [5.1]
Pre-eclampsia [including HELLP], *n* [% of cases]	6 [5.3]	1 [12.5]	7 [6]
Infectious maternal complications during pregnancy which required antibiotics, *n* [% of cases]	8 [7.1]	0 [0]	8 [6.8]
- Pneumonia	1 [0.9]	0 [0]	1 [0.85]
- Cystitis	4 [3.5]	0 [0]	4 [3.4]
- Gastroenteritis	2 [1.8]	0 [0]	2 [1.7]
- STD	1 [0.9]	0 [0]	1 [0.85]

IQR, interquartile range; PIH, pregnancy-induced hypertension; HELLP, haemolysis, elevated liver enzyme levels, and low platelet level; STD, sexually transmitted diseases.

any additional treatment. In two other pregnancies TG was ceased after the flare as the therapeutic effect was judged to be apparently insufficient, precluding unnecessary use during further pregnancy. The median maternal 6-TGN level during pregnancy was 464 pmol/10^8 RBC [*n* = 33, IQR 288–633.5].

Ten pregnancies resulted in a first-trimester miscarriage [8.5%] and one patient had an induced abortion due to trisomy 21 of the fetus, at the age of 39.

One pregnancy resulted in a stillbirth at 22 weeks. Chorionic villus sampling was performed because of a thickened nuchal fold and revealed no chromosomal abnormalities. During this pregnancy, repeated vaginal bleedings resulted in a haemoglobin level of 4.9 mmol/l in this subject. Around 20 weeks' GA, a premature rupture of membranes occurred, resulting in a stillborn baby of 314 g.

Most patients [*n* = 72, 69%] had a vaginal delivery. In 33 of the 105 completed pregnancies [31%], a caesarean section was performed: 18 were elective and 15 occurred in an emergency setting. In 10 cases, the indication for an elective caesarean section was related to the underlying IBD, ie, perianal disease. In the other eight patients, the indications were: placenta praevia [*n* = 1], previous caesarean section [*n* = 3], preeclampsia [*n* = 2], and unknown [*n* = 2]. The indications for an emergency caesarean were: fetal distress [*n* = 6], obstructed labour [*n* = 4], severe preeclampsia [*n* = 3], labour prior to the scheduled caesarean due to perianal disease [*n* = 1], and unknown [*n* = 1].

3.3. Neonatal outcomes

The median gestational age of the singleton newborns was 39 weeks [IQR 38–40 weeks] with a median birthweight of 3355 g [IQR 2965–3726 g]. One neonate was born with a cleft palate. During pregnancy, this neonate had been exposed to both adalimumab and TG and no genetic cause was detected. The median gestational age of the twins was 37 weeks with a median birthweight of 2470 g [IQR 2400–2510 g]. None of them had congenital abnormalities. Additional neonatal characteristics are provided in Table 2.

There was a trend towards higher prematurity [17.6%] and SGA [23.5%] rates in singleton pregnancies with active disease compared with those in remission [9.8% and 7.7%, respectively], with odds ratios of 1.98 [95% CI 0.47–8.41] and 3.69 [95% CI 0.91–14.92] respectively.

Admission to the neonatal intensive care unit was indicated in eight newborns [7%] for the following indications: prematurity [*n* = 6], glucose monitoring/ neonatal hypoglycaemia [*n* = 1], or disturbances in the normal transitional process [*n* = 1]. Seventeen neonates [16%] were admitted to the neonatology ward unit for a variety of indications: prematurity [*n* = 4], glucose monitoring/ neonatal hypoglycaemia [*n* = 6], jaundice [*n* = 2], disturbances in the normal transitional process [*n* = 1], a suspected infection [*n* = 1], moaning and transient hypotonia [*n* = 1], observation because of a positive group B streptococcus [GBS] test [*n* = 1], and intrauterine exposure to TG [*n* = 1].

One of the newborns, initially admitted due to hypoglycaemia, developed hematochezia with an international normalised ratio [INR] of prothrombin time of 2.0 with a normal platelet count. After correcting the elevated INR with 1 mg of vitamin K, the rectal blood loss resolved, comprising a differential diagnosis including a Meckel's diverticulum, colitis [either infectious, allergic, or caused by cytomegalovirus], or coagulopathy. Although this newborn developed a transient thrombocytopenia with a platelet count of 54 × 10^9/l, the rectal blood loss did not re-occur. In nine other newborns, the paediatrician was consulted mostly routinely due to maternal medication use [*n* = 8].

Table 3. Outcomes compared with Dutch reference populations.

	Our cohort [singleton and twin pregnancies]	Our cohort [only singleton pregnancies]	Jharap *et al.* [2014][15]	Kanis *et al.* [2017][18]		Kanis *et al.* [2021][17]		Perined [2020][19]
	Thioguanine [*n* = 117]	Thioguanine [*n* = 113]	Thiopurines [*n* = 41]	Thiopurines [*n* = 146]	Non-exposed [*n* = 263]	Thiopurine monotherapy [*n* = 240]	Non-exposed [*n* = 564]	General Dutch population [*n* = 159 582]
Miscarriages [%]	10 [8.5]	10 [8.8]	7 [17]	35 [24.0]	43 [16.3]	-	-	-
Number of live-born children	109	101	31	108	203	240	564	159 582
Twin pregnancies	4 [7.3% of infants]	0	1 [6.4 % of infants]	-	-	Max 8[a]	Max 8[a]	0
Disease activity during pregnancy per live birth [%]	17 [15.6]	17 [16.8]	-	31 [28.7]	69 [34.7]	45 [19]	145 [26]	-
Birthweight in g, median [IQR]	3294 [2810–3696]	3355 [2965–3726]	3410 [3200 –3680]	3360 [3018–3630]	3326 [2898–3640]	3300 [3000–3600]	3300 [3000–3700]	3000–3499
Gestational age in weeks, median [IQR]	39 [37.9–40]	39 [38–40]	39 [38–40.1]	38.6 [37.4–40]	39.0 [38–40]	39 [38–40]	39 [38–40]	39 [38–40]
Preterm birth, *n* [% of infants]	16 [15.1, *n* = 106]	10 [10.2, *n* = 98]	3 [9.7]	12 [11.4]	21 [10.4]	33 [14]	61 [11]	8148 [5.1]
Small for gestational age [%]	13 [12.6, *n* = 103]	10 [10.5, *n* = 95]	-	[b]	[b]	[b]	[b]	14 422 [9.04]
Low birthweight [%]	10 [9.7, *n* = 103]	6 [6.3, *n* = 95]	-	10 [9.4]	21 [10.4]	-	-	6791 [4.3]
Congenital abnormalities in live-born children [%]	1 [0.9]	1 [1]	2 [6.5]	4 [3.9]	4 [2.1]	8 [3]	10 [2]	854 [0.54]
Caesarean section [%]	33 [30]	31 [31]	14 [47]	-	-	75 [32]	142 [25]	26 998 [16.9]

IQR, interquartile range; Max, maximum.
[a]1000 live-born children included in this study, not specified in which subgroup the twin pregnancies occurred.
[b]Could not be determined due to the use of different definitions of small for gestational age.

Laboratory testing for myelosuppresion in either umbilical cord blood or neonatal vein puncture was performed routinely in 16 neonates. Two of the tested neonates [13%] had anaemia at birth [Hb 8.3 and 7.4 mmol/L, respectively] and none had thrombocytopenia or leukopenia at birth. Umbilical cord 6-TGN concentration was only measured in one newborn [224 pmol/10^8 RBC]; the corresponding maternal 6-TGN concentration was not available. In 98 pregnancies, TG was continued after birth and breastfeeding was given to 38% of these children, without any reported complications. During one pregnancy TG was stopped at 28 weeks' GA at patient request due to a breastfeeding wish; the reason why the other patients did not breastfeed was not reported.

3.4. Comparison with Dutch reference populations

Our outcomes were compared with the general Dutch population and with data from three Dutch cohort studies on the use of conventional thiopurines in pregnant IBD patients [Table 3.].[15,17–19] Due to the relatively high percentage of twins [7.3%] in our cohort and the fact that twin pregnancies are associated with adverse maternal and neonatal outcomes, both singleton pregnancies [*n* = 113] and all pregnancies [*n* = 117] were compared separately with the aforementioned reference populations.[20] Neonatal outcomes matched with our rate of congenital abnormalities, birthweight, and gestational age at birth [Table 3.]. In addition, the rate of miscarriages, flare of disease activity, and rate of caesarean sections were comparable to our cohort [Table 3.].

4. Discussion

In this extended case series, the use of TG during pregnancy in IBD patients was not in excess associated with adverse maternal or neonatal outcome compared with cohort studies on the use of conventional thiopurines in pregnant IBD patients or the general population.

Conventional thiopurine treatment with AZA or MP during pregnancy in IBD patients is considered to be responsibly safe.[4] Since the effector metabolites are similar for all thiopurines, but less additional metabolites are formed during the conversion of TG, a comparable impact on pregnancy outcome could be expected. In our study, the risk of a premature delivery in the singleton pregnancies [10%] was comparable to the risk reported in a study including 1712 pregnant IBD patients, in which 10% of the non-exposed and 13% of the conventional thiopurine exposed singleton pregnancies was a preterm delivery.[3] In a Dutch study including 1000 children born to mothers with IBD, a similar risk of premature delivery was observed in both non-exposed [11%]

and thiopurine-exposed [14%] patients, succesively.[17] Since the risk of SGA is highly dependent on the reference population, we decided to compare our results only with Dutch populations.[21] In the previously mentioned Dutch study, 3% of the thiopurine-exposed and 4% of the non-exposed children were born SGA, which is lower than the SGA rate in our cohort [10.5%].[17] This difference is most likely caused by the use of a different and older Dutch reference curve and a different definition of SGA, namely a weight below 2 SD for gestational age.[22] When we used the same definition and curve, in our population none of the children was born SGA, which would suggest that TG exposure in IBD patients is not associated with an increased risk of SGA. Moreover in the general population in The Netherlands, the risk of SGA in singleton pregnancies is 9%, which is more in line with our findings.[19]

The rate of congenital malformations among the live-born children in our cohort, namely one cleft palate, was lower than the pooled incidence rate of 2.1% found in a recent meta-analysis including infants born to women with IBD.[23] A Dutch study, including 1000 children born to mothers with IBD, observed that 3.3% of the thiopurine-exposed children had a congenital abnormality, which was comparable [$p = 0.2$] to the 1.8% found in the non-exposed children.[17] Comparable to intrauterine exposure to conventional thiopurines,[3,17] intrauterine exposure to TG is in this series not associated in excess with abnormalities.

The rate of gestational diabetes in our cohort was comparable to the 5% prevalence reported in Europe, and the risk of a caesarean section was similar to the incidence reported in literature.[3,24–26] A retrospective single-centre cohort study performed in The Netherlands observed that the incidence rate of preeclampsia varied between 6.2% and 8.2%, depending on the used definition.[27] The rate of pre-eclampsia in our cohort was comparable to both the Dutch study and the incidence rate in Europe [5.3%].[28]

Of the pregnant women in our case series, 7% had an infectious complication requiring antibiotics, which is much lower than the observed percentage by a drug utilisation study in The Netherlands, which observed that 21% of all pregnant women were prescribed at least one antibiotic.[29] We cannot rule an under-reporting of infectious complications in our study, even though we asked the treating physician who shared the data whether there were any medication changes during pregnancy. It remains possible that antibiotics were prescribed by the general practitioner without the knowledge of the gastroenterologist or gynaecologist. This makes it difficult to determine the precise maternal infection risk during TG therapy in our case series, although it is reassuring that none of the pregnant women needed to be admitted for an infection.

Primarily due to different definitions used in studies, the risk of neonatal anaemia, thrombocytopenia, and leukopenia after intrauterine exposure to conventional thiopurines differs among studies. One study observed a neonatal anaemia rate of 60% [Hb < 10 mmol/L] and another observed a rate of 6% [Hb < 8.4 mmol/L].[15,30] If we applied definitions similar to the ones applied in these studies, we calculated rates of 31% and 13%, respectively. The precise incidence of neonatal anaemia remains, however, difficult to determine since normal haemoglobin ranges of neonates are lacking due to ethical concerns of drawing blood from neonates to determine such ranges; therefore reference ranges are used. This makes it difficult to decide if intrauterine exposure to both conventional thiopurines and TG gives a true risk of myelotoxicity in neonates.

Breastfeeding was infrequently given in this cohort compared with the 69% breastfed children in the general Dutch population.[31] A possible explanation might be a maternal fear of potential harmful effects to the infant or negative advice from the medical specialist due to a lack of data. Studies concerning the safety of maternal conventional thiopurine use described that breastfeeding is considered to be safe and is to be recommended due to beneficial effects, even though low concentrations of thiopurine metabolites could be detected in breast milk.[32–34] Since TG has the same active metabolites one may assume that breastfeeding during TG treatment is safe, although data are lacking.

In this study a relative large cohort is represented, but we need to acknowledge several limitations. First, the inclusion of multiple pregnancies from the same individual [15%] could induce bias. Second, because of the design of the study, disease activity at conception was not documented and also dosage of medication was not calculated in mg/kg since data on maternal weight at conception were not registered consistently. Furthermore, in this series a formal control group with IBD patients treated with conventional thiopurines and a non-IBD control group are lacking, which makes it challenging to interpret our results. However, recently large, prospective studies about the safety of conventional thiopurines during conception and pregnancy have been published, including studies with a [comparable] Dutch population. This makes it possible to [indirectly] compare our results with existing literature and, as far as possible with a case series, draw a conclusion about the safety of TG during conception and pregnancy. Since maternal 6-TGN levels are only determined in 33 women, no firm conclusions can be drawn about the association between these levels and the occurrence of maternal and/or neonatal complications. We also recognise the probable existence of missed and therefore unreported cases. The under-reporting of miscarriages is also likely, since very early pregnancies might not be reported to the treating physician and miscarriages may occur before women know about a pregnancy.[35] Moreover in the majority of neonates, follow-up was relatively short term and therefore nothing can be said about the long-term health outcomes.

In conclusion, intrauterine exposure to TG is not associated in excess with adverse maternal or neonatal outcomes. Follow-up data of the exposed children are needed to determine the long-term health outcomes.

The data underlying this article will be shared on reasonable request to the corresponding author.

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Conflict of Interest

FC, MAdB, CJJM, EMvA, RHC, CSH, MCV, ALMW, MLS, BJ, IA, PJB, GJT, LW, MWMDL, PGAvB, MK, MGVMR, FH, MEB, WAvD, JW, MMPJAvdV and HJCB have nothing to declare. MS has received an unrestricted research grant from TEVA. DPvA served as speaker, adviser, and/or principal

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Author Contributions

FC, MS, MAdB, CJJM, and NKdB contributed to the design of the study. FC, MS, CJJM, EMvA, RHC, DPvA, AAvB, CSH, MCV, ALMW, MLS, BJ, FDMvS, IA, PJB, GJT, HL, LW, MWMDL, PGAvB, LPLG, MK, MGVMR, FH, MEB, JPK, PWJM, WAvD, JW, MMPJAvdV, and NKdB identified and included patients. FC analysed the data. FC drafted the manuscript. All authors critically revised the manuscript for important intellectual content. All authors approved the final version of this manuscript.

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Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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