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PREGNANCY AND DRUG

Pregnancy outcome following in utero exposure to azathioprine: A French comparative observational study

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Summary
Aim of the study. — To evaluate whether azathioprine exposure during pregnancy increases the risk of birth defects and prematurity.
Method. — Prospective comparative observational study using the French pregnancy database TERAPPEL. To evaluate birth defects, outcomes of pregnancies exposed to azathioprine during the 1st trimester were prospectively assessed and compared to that of pregnancies exposed to another drug used for the same indications. Secondly, the rate of preterm births was compared between fetuses exposed to azathioprine at least during the third trimester and those exposed during the first trimester only.

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Results From 447 requests for a risk assessment for women receiving azathioprine during pregnancy, 193 pregnancies meet inclusion criteria. One hundred and twenty-four of them were exposed to azathioprine during the 1st trimester and were compared to that of 124 pregnancies exposed to another drug used for the same indication. Azathioprine use during the first trimester was not statistically associated with the risk of all birth defects ([7.3% vs. 5.4%]; [OR = 1.36; 95%CI: 0.44—4.20]) nor with major birth defects (5.2% vs. 1.8% [OR = 2.96; 95%CI: 0.56—15.64]). The rate of preterm births (22.5% vs. 27.3%, $P = 0.579$) was similar regardless of the exposure period to azathioprine (at least during the third trimester or during the first trimester only).
Conclusions. — This study confirms that first trimester exposure to azathioprine is not associated with an elevated rate of birth defects and that the high rate of preterm births among women exposed to azathioprine is probably explained by the underlying maternal disease.

Abbreviations

6-MP6	mercaptopurine
6-MMP	methylmercaptopurine
6-TGN	6-thioguanine
AZA	azathioprine
CNIL	French national commission of informatics and liberties
DNA	deoxyribonucleic acid
GW	gestational weeks
IBD	inflammatory bowel diseases
ICD	International classification of diseases
LBW	low birth weight
LMP	last menstrual period
RNA	ribonucleic acid

Introduction

Azathioprine (AZA), a purine analog, is used in the treatment of autoimmune disorders, such as inflammatory bowel diseases (IBD) and as part of immunosuppressive regimens to prevent transplant rejection [1—4]. After oral administration, AZA is quickly converted to 6-mercaptopurine (6-MP), which is further metabolized leading to the formation of 6-thioguanine (6-TGN), 6-methyl-MP (6-MMP) and thiouric acid [5]. AZA and 6-TGN cross the placenta, whereas 6-MMP does not [6,7]. Animal studies have shown that AZA can lead to congenital abnormalities, such as limb defects, ocular anomalies and cleft palate [8—11]. The summary of product characteristics of azathioprine for pregnancy says that ''AZA can cause fetal harm when administered to a pregnant woman and should not be given during pregnancy without careful weighing of risk versus benefit. Whenever possible, its use in pregnant patients should be avoided''. Nevertheless, data from humans suggest a risk in third trimester but also that the benefit of treatment for the mother outweighs the potential risk for the fetus and newborn [12].

Studies examining the effect of maternal AZA exposure on pregnancy outcome report conflicting results, but a lot of data suggest that thiopurines have little effect, if any, on the fetus [13—23]. In addition, the deleterious consequences on both the mother and fetus of any disease relapse resulting from the discontinuation of thiopurine during pregnancy should be taken into consideration [24,25].

Thus, the primary objective of this study was to compare the rate of all and major birth defects in fetuses exposed in utero to AZA during the first trimester of pregnancy and in those exposed to another immunosuppressant used for a similar indication. It is often impossible to determine whether the high rate of low birth weight (LBW) and prematurity among babies born to AZA-treated women result from treatment or maternal illness because AZA is used to treat women with severe illness. Thus, the secondary endpoint was to compare the birth weight and gestational age at delivery of infants exposed in utero to AZA during the first trimester only and those exposed at least during the third trimester.

Methods

All requests for risk assessment for AZA exposure during pregnancy registered in the French pregnancy database between 1 January 1989 and 15 May 2012 were selected.

Data were obtained from requests made by physicians or patients asking to a French regional pharmacovigilance center to carry out a risk assessment for drug exposure during pregnancy. All these requests are recorded in the French pregnancy database TERAPPEL approved by the French National commission of informatics and liberties (CNIL), registered under the number: 816—257 [26]. Women were informed about the computerization of their data and could oppose it. Collected information included maternal age, gravidity, parity, the number of previous spontaneous and induced abortions, smoking and alcohol consumption habits, drug(s) dose, indication, and maternal medical history, duration of pregnancy using the date of the last menstrual period (LMP) or the date of conception estimated from ultrasound examination. Data on the outcome of pregnancy was obtained after the expected date of delivery from structured telephone interviews and/or questionnaires mailed

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to the mother and/or her physician after she had provided informed verbal consent. The collected data consisted of detailed information about the outcome of the pregnancy, including neonatal complications, birth weight, physical findings and the presence of birth defects.

Risk of birth defects

The exposed group (G1) comprised pregnant women who had been exposed to AZA at least during the organogenesis period (from 4 to 12 weeks after LMP), if the first request for risk assessment had been received within 22 weeks of LMP (i.e. before the level II ultrasound scan) and if follow-up data on pregnancy outcome were available. The outcome of fetuses exposed to AZA during the first trimester was prospectively assessed.

The control group (C) consisted of pregnant women randomly selected from the same database who had been exposed during the organogenesis period (from 4 to 12 weeks after the LMP) to another drug or immunosuppressant used for the treatment of Crohn's disease, ulcerative colitis, organ transplant, multiple sclerosis, systemic lupus erythematosus, Behçet's disease, pemphigus or nephrotic syndrome (such as mesalazine, corticosteroids, sulfasalazine, hydroxychloroquine or beta interferon, except for mycophenolate mofetil because his known teratogen effects). All other inclusion criteria for the control group were identical to those of the AZA group (G1), i.e. the first request for risk assessment was made within 22 weeks of LMP and follow up data on pregnancy outcome were available. The outcome of control pregnancies was also prospectively assessed.

For the purpose of this study, the gestational age was calculated from the date of LMP. We defined miscarriage as the loss of an embryo or fetus before 22 gestational weeks (GW). Stillbirth was classified into two groups: loss of a fetus after 22 GW (i.e. the fetus died during pregnancy) was recorded as fetal death in utero; and death of a fetus who was alive at the beginning of delivery was recorded as fetal death during delivery. Birth defects were classified as major or minor abnormalities by a clinical geneticist, who was blind to the drug exposure status. Major birth defects were those with serious medical, surgical, or cosmetic consequences, including significant neurological and/or developmental damage [27]. The rate of all and major birth defects were calculated according to the methodological considerations of Schaefer et al. [28]. Birth defects include genetic syndromes and chromosomal abnormalities, but both these types of abnormalities were excluded from the calculation of the birth defect rates. The crude miscarriage rate was calculated after the exclusion of elective abortions [29]. The group exposed to AZA during organogenesis (G1) was compared to the control group (C) to estimate the risk of birth defects.

Risk of preterm birth and low birth weight

We compared two other exposed groups (G2 and G3) to assess whether AZA exposure can increase the risk of preterm birth or LBW. The first group (G2) was derived from G1 and included pregnant women who stopped AZA during or at the end of the first trimester. The second group (G3) included pregnant women who received AZA at least during the third trimester and up to delivery.

Preterm birth was defined as delivery at less than 37 gestational weeks after the exclusion of twin pregnancies. LBW was defined as a birth weight lower than 2500 g, regardless of gestational age. LBW following twin pregnancies was not included. All comparisons included live births only and excluded births with missing data on gestational age or birth weight. To evaluate the risk of preterm birth and LBW, the recorded gestational age and birth weight at delivery were compared between infants exclusively exposed to AZA during the first trimester (G2) and those exposed to AZA during at least the third trimester (G3).

Statistical analysis was performed using SPSS vs. 13.0 statistical software for Windows (Inc., Chicago, IL). Descriptive data were compared using the Student's t test for two groups. Categorical data were expressed as a percentage and compared using the chi^2 test or the Fisher exact test when the chi^2 test was not applicable.

Results

Between 1 January 1989 and 15 May 2012, 447 requests for a risk assessment for women receiving AZA during pregnancy were recorded. The selection of data is described in detail in a flow chart (Fig. 1).

Risk of birth defects

Among these 447 requests, 124 (28%) pregnancies exposed to AZA during the first trimester met inclusion criteria for the evaluation of birth defects (G1). For the control group (C), 124 pregnancies were selected randomly. Overall, 72/124 (58.1%) women were exposed to AZA during the first trimester only, 8/124 (6.4%) during the first and second trimesters, and 44/124 (35.5%) throughout pregnancy. For fetuses exposed during the first trimester only, the median duration of AZA exposure was 8 weeks of gestation (range 5 to 12). In 88 (71%) women, AZA was associated with other drugs (other immunosuppressants in 43.5%), whereas AZA was the only drug used in the remaining 36 (29%) women. When specified (60/124), AZA was administered at a median dose of 100 mg per day [50—150 mg]. Maternal characteristics and data about diseases of the AZA and control group (C) are shown in Table 1. Maternal characteristics were similar in the two groups, but women from the AZA (G1) group were more frequently treated with AZA for Crohn's disease or organ transplantation, and less frequently for ulcerative colitis or multiple sclerosis than those in the control group. The mode of delivery and pregnancy outcome are compared in Table 2. The rate of live births was lower in the AZA group than in the control group (73% vs. 85.7%, respectively; $P < 0.05$). There were no significant differences in the rate of miscarriages, ectopic pregnancies or stillbirths between groups, but the crude rates of voluntary abortion and intrauterine death were slightly, but not significantly, higher in the AZA than in the control group. Therapeutic abortions were performed either for maternal causes or after the in utero diagnosis of abnormalities. The rate of all birth defects [(7.3% in the AZA group vs. 5.4% in the control group); (OR = 1.36; 95% CI: 0.44—4.20); $P = 0.589$] and the rate of major birth defects [(5.2% in the AZA group vs.

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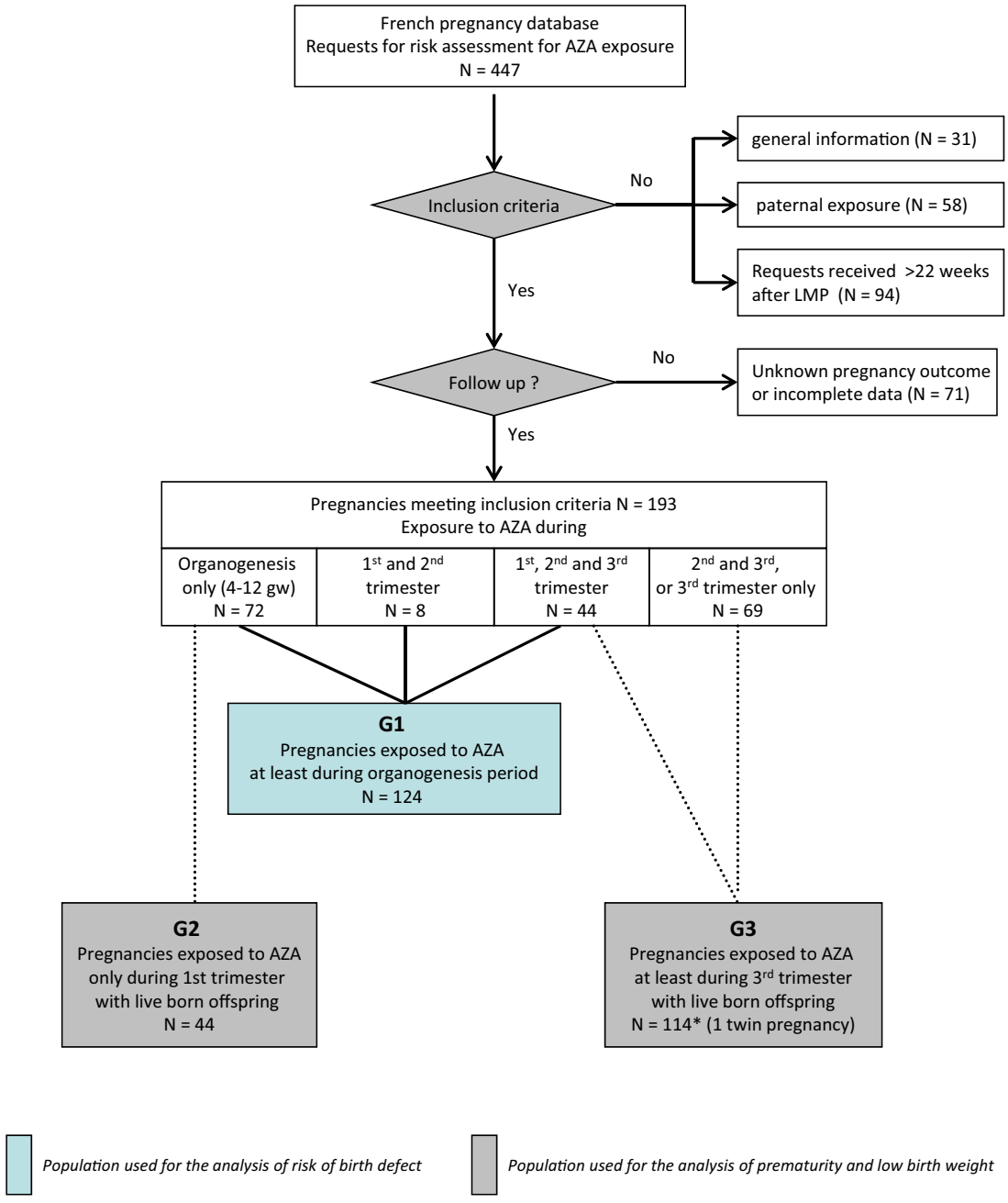

Figure 1. Population used for the analysis of risk of birth defect and for the analysis of prematurity and low birth weight.

1.8% in the control group (OR = 2.96; 95% CI: 0.56—15.64; $P = 0.255$)] did not significantly differ between the AZA and control group (Table 3).

Details on the seven major and six minor birth defects observed in the two groups are provided in Table 4. Therapeutic abortion was performed in five cases (four in the AZA group and one in the control group).

Risk of prematurity and low birth weight

Among the 193 cases of exposure to AZA during pregnancy, 72 involved exposure during the first trimester only, of which 44 led to live births (G2), and 113 (including a twin pregnancy) involved exposure to AZA at least during the third trimester and until delivery (G3). The data on live births in both groups are presented in Table 5. The duration of pregnancy was identical in the two groups (both 37.8 weeks, $P = 0.848$). The rate of preterm births among the 114 neonates from the late pregnancy AZA group (G3), was 22.5% and did not differ significantly from that observed in the early pregnancy AZA group (G2) [27.3%; $P = 0.579$]. The average weight of live neonates ($P = 0.518$) and the percentage of LBW ($P = 1$) at term were also comparable between the two groups.

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Table 1 Comparison of maternal characteristics between AZA (G1) and control (C) groups.

Maternal characteristics	AZA group (G1) $n = 124$	Control group (C) $n = 124$	*P*
Maternal age (year) [mean ± SD]	30.1 ± 5.4	31 ± 4.9	*0.204*
Concomitant drugs (%)			
AZA alone	36/124 (29)		—
Other immunosuppressants	54/124 (43.5)	70/124 (56.5)	
Other drugs	34/124 (27.5)	54/124 (43.5)	
Multigravida (%)	47/84 (56)	60/97 (62)	*0.451*
Multipara (%)	33/79 (41.8)	52/95 (54.7)	*0.088*
Previous spontaneous abortions (%)	7/69 (10.1)	13/93 (14)	*0.463*
Gestational age at call (weeks)	9.8 ± 6.5	10.6 ± 8.6	*0.452*
Maternal disease			
Inflammatory bowel disease (IBD)	64 (52)	54 (44)	*0.143*
Crohn's disease	54 (44)	26 (21)	***< 0.001***
Ulcerative colitis	10 (8)	28 (23)	*0.002*
Organ transplantation	18 (15)	3 (2)	***< 0.001***
Multiple sclerosis	9 (7)	34 (27)	***< 0.001***
Others	33 (27)	33 (27)	1

AZA: azathioprine. Italics is for head of data.

Table 2 Pregnancy outcomes in the AZA (G1) and control (C) groups.

	AZA group (G1) $n = 124$ (%)	Control group (C) $n = 124$ (%)	*P*
Multiple pregnancy[a]	3/124 (2.4)	2/124 (1.6)	
Pregnancy outcomes			
Miscarriage, < 22 GW	5/101[b] (4.9)	4/111b (3.6)	*0.739*
Ectopic pregnancy	1/124 (0.8)	0/124 (0)	
Voluntary abortion	16/124 (12.9)	9/124 (7.2)	*0.140*
Medical abortion	7/124 (5.6)	4/124 (3.2)	*0.355*
Maternal cause	2/7	2/4	
Fetal cause	5[d]/7	2d/4	
In utero fetal death, > 22 GW	4/127 (3.2)	1/126 (0.8)	*0.370*
Fetal death during delivery	1/127 (0.8)	0/126 (0)	
Live birth	92/126[c] (73)	108/126 (87.8)	***0.002***
Mode of delivery	$n = 91$[c]	$n = 106$	
Not known	17/91 (18.7)	32/106 (30.2)	
Vaginal	44/91 (48.4)	47/106 (44.3)	
Instrumental	4/91 (4.4)	3/106 (2.8)	
Cesarean section	26/91 (28.6)	24/106 (22.6)	

AZA: azathioprine; GW: gestational weeks. Italics is for head of data.
[a] All multiple pregnancies were twins.
[b] Crude miscarriage rate was calculated after the exclusion of elective abortions.
[c] One multiple pregnancy was voluntarily aborted.
[d] One medical abortion for chromosomal abnormalities in each group.

Discussion

In our study, the rate of major birth defects in the AZA group was not statistically different from that in the control group, but the crude rate (percentage) of major birth defects was three times as high as the rate in the control group. However, our sample size was small and a larger study is required to confirm this finding. In French healthy mothers, congenital abnormalities occur in 2% to 3% of pregnancies [30,31]. In this study, both groups had birth defect rates higher than the expected baseline risk. This can probably be explained by a pregnancy outcome more easily obtained in cases of fetus malformation. Another explanation may be the severity of the maternal disease, the comorbidities among some expectant mothers of our study (graft, etc.) and the numerous drugs taken during their pregnancy. Exposure to AZA

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Table 3 Birth defects in the AZA (G1) and control (C) groups.

	AZA group (G1) $n=97$[a]	Control group (C) $n=111$[b]	*P*	OR	95% CI
All birth defects	8/97	7/111			
Chromosomal abnormalities	1[c]/97	13/111			
Birth defects	7/97	6/111			
Major	5/97	2/111			
Minor	2/97	4/111			
Rate of all birth defects[d]	7/96 (7.3%)	6/110 (5.4%)	0.589	1.36	[0.44—4.20]
Rate of major birth defects[d]	5/96 (5.2%)	2/110 (1.8%)	0.255	2.96	[0.56—15.64]
Type of birth defects[d]					
Reno-urinary tract	2	3			
Heart	1	1			
Brain	0	2			
Skeletal	2	0			
Multiple	2	0			

AZA: azathioprine.
[a] Including live births (92) and fetal anomalies leading to the elective termination of pregnancy (5).
[b] Including live births (108), fetal anomalies leading to the elective termination of pregnancy (2) and fetal death (1).
[c] Down syndrome (1 in each group).
[d] After exclusion of chromosomal abnormalities.

was not associated with a specific pattern of major birth defects. Indeed, in the two cases of multiple malformations in the AZA group, the role of other drugs received by the mother (pravastatin in one, and pyridostigmine and ambemonium for myasthenia gravis in the other) cannot be ruled out. Furthermore, both fetuses with reno-urinary tract malformations were born to mothers who were concomitantly treated with AZA and tacrolimus after organ transplantation. This may be a coincidental finding because neither AZA nor tacrolimus have been associated with urinary tract malformations [32,33]. Our findings are comparable to those of other studies involving pregnant women treated with AZA/6-MP for IBD [14—16,24,34,35]. However, a study suggested that AZA exposure increases the risk of atrial and ventricular septal defects (adjusted OR: 3.18; 95% CI: [1.45—6.04]) [36]. However, the authors also acknowledged that these findings may reflect the underlying maternal disease. Another study [17] also found a higher risk of congenital abnormalities in AZA-exposed women than in non-exposed healthy controls (RR: 2.3; 95% CI: [1.0—5.2]), but after adjustment for maternal disease, the RR decreased to 1.1 (95% CI: [0.5—2.9]). Overall, it appears that exposure to AZA does not increase the risk of congenital abnormalities; instead, maternal disease appears to be a confounding factor in most studies [37]. This is indirectly supported by Dominitz and al. [38], who demonstrated that congenital malformations are more commonly recorded in infants born to mothers with Crohn's disease than in those born to women without IBD, but not in those born to mothers with ulcerative colitis.

The rate of vaginal deliveries was higher than that of cesarean sections in our two groups. This finding contrasts with a meta-analysis reporting that the rate of cesarean sections is 1.5 times higher in IBD patients than in controls [39]. This discrepancy may be explained by the inclusion of women with other pathological conditions besides IBD treated with azathioprine in our study. The rate of live births was significantly lower in the AZA than in the control group (72.4% vs. 85.5%, respectively; $P=0.013$) because of the higher rates of voluntary and medical abortion and intrauterine fetal death in the AZA group. The use of AZA is not recommended during pregnancy and the SPC states that ''AZA can cause fetal harm when administered to a pregnant woman''; this may explain the high rate of voluntary abortion in the AZA group. Another explanation is the severity of the disease among expectant mothers, because more women in the AZA group than in the control group received treatment for an organ transplant. The rate of fetal death (3.2%) in the AZA group (G1) is higher than that reported in the general population. In a recent review, the rate of stillbirths was 2.3% for female kidney transplant recipients receiving AZA and/or prednisone and 2.4% for those receiving cyclosporine [40]. In the four cases of fetal death recorded in our study, three women received AZA for transplantation (two kidney and one heart transplant). The occurrence of fetal death was probably linked to a maternal disease in three cases (organ rejection during pregnancy, premature rupture of membranes at 29 weeks and isthmus incompetent cervix). None of these 4 fetuses had any major malformations. Finally, the rate of medical abortion because of causes related to the fetus was also slightly higher in the AZA than in the control group (5/124 vs. 2/124, respectively) because more congenital malformations required medical abortion (4 vs. 1) in this group. The overall rate of miscarriage in the general population ranges from 15 to 20% [41]. In our study, the miscarriage rate was low (only 4.5%), which is probably explained by the relatively late gestational age at call (9.8 ± 6.5 weeks and 10.6 ± 8.6 weeks respectively) such that many early miscarriages would have been missed.

The secondary endpoint of the present study was to compare the rate of preterm birth and LBW depending of the exposure period to azathioprine. The rate of preterm birth in the general population is estimated at about 7.6% [42],

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Table 4 Description of major and minor birth defects observed in the AZA (G1) and control (C) groups.

Major birth defects	Exposure	Indication (dose)	Other drugs	Pregnancy outcome
AZA group (G1)				
Cardiac birth defects: ventricular and atrial septal defects with Ebstein malformation. Hypoplasia of the pulmonary artery trunk and probable pulmonary valve atresia	Azathioprine throughout pregnancy	Crohn's disease (unknown)	Corticosteroid	Live birth
Urinary tract birth defects: megacystis and mega ureter. Long philtrum and single umbilical artery	Azathioprine up to week 12	Organ transplantation (50 to 100 mg/d)	Tacrolimus 50 to 100 mg/day Atenolol	Medical abortion at 15 GW
Urinary tract birth defects: posterior urethral valves Renal hypoplasia with probable megacystis Dysplasia microretrognathism with small left ear and low nasal bridge marked	Azathioprineup to week 12 —	Organ transplantation (unknown)	Tacrolimus Aspirin Corticosteroid	Medical abortion at 18 GW
Multiple malformations: dolichocephaly, retrognathism Syndactylies of fingers and toes Malposition and external rotation of the left kidney Ambiguous external genitalia, talipes equino-varus, large unilateral adrenal gland	Azathioprineup to week 16	Myasthenia (75 mg/d)	Insulin Pyridostigmine Ambenonium	Medical abortion at 16 GW
Multiple malformations: cleft lip and palate, narrow thorax Agenesis of the tibias, valgus feet Hyperechoic and enlarged kidneys	Azathioprine up to week 22	Organ transplantation (50 mg/d)	Tacrolimus Corticosteroid Pravastatine Pantoprazole	Medical abortion at 24GW
Control group (C)				
Nervous system: cerebral birth defects Acrania, lymphedema	Ambenonium up to week 12	Myasthenia	Paroxetine Vitamin B12	Medical abortion at 12 GW
Nervous system: cerebral birth defects Aneurysm of the great cerebral vein (of Galen)	Mesalazin throughout pregnancy	Ulcerative colitis	None	Live birth

Minor birth defects	Exposure	Indication (dose)	Other drugs	Pregnancy outcome
AZA group (G1)				
Renal duplication with only 1 ureter	Azathioprine throughout pregnancy	Crohn's disease (unknown)	Prednisolone 40 mg/day	Live birth
Cystic mass of sacrum	Azathioprine throughout pregnancy	Crohn's disease (50 mg/d)	Infliximab	Live birth
Control group (C)				
Bilateral pyelectasia	Mesalazin 2 g/d (1st trimester)	Crohn's disease		Live birth
Bilateral uretero-hydronephrosis	Prednisone throughout pregnancy	Myasthenia	Pyridostigmin Ambenonium Paroxetin	Live birth
Right hydronephrosis and left pyelic ectasia. Nose anomaly	Prednisone throughout pregnancy	Lupus erythematosus	Fluindion Enoxaparin	Fetal death
Aortic stenosis without ventricular asymmetry	Prednisone 5 mg/d (1st and 2nd trimester)	Lupus erythematosus	Hydroxy-chloroquine 400 mg/d	Live birth

AZA: azathioprine; GW: gestational weeks.

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Table 5 Comparison between outcomes of live births after maternal use of AZA in early and late pregnancy.

	AZA in early pregnancy[a] (G2) $n = 44$[c]	AZA in late pregnancy[b] (G3) $n = 114$[c]	*P*
Sex ratio (F/M)	0.90 (19/21)	0.83 (51/61)	–
Mean gestational age at delivery (w)	37.8 ± 3.1	37.8 ± 2.4	*0.848*
Prematurity < 37 weeks	9/33 (27.3%)	23/102 (22.5%)	*0.579*
32 to 36 weeks	8/33 (24.2%)	20/102 (19.6%)	
< 32 weeks	1/33 (3%)	3/102 (2.9%)	
Mean weight of live births (g)	3004 ± 665	3 042 ± 555	
[Min-Max]	[570–4450]	[1710–4790]	*0.727*
Low birth weight (%)	5/42 (12%)	19/108 (17.6%)	*0.394*
Mean weight of full term newborns (g)	3169 ± 418	3 233 ± 453	*0.518*

AZA: azathioprine.
[a] AZA exposure only during the first trimester.
[b] AZA exposure at least during the third trimester and until delivery.
[c] Number of lives births.

but was much higher in our patients, reaching 22.5% and 27.3% in the late and early pregnancy AZA groups, respectively. Therefore, our study shows that the occurrence of preterm birth and LBW are comparable between fetuses exposed early in utero to AZA (only in Q1) and those exposed at least during the third trimester (throughout pregnancy for 44/114). Although factors contributing to preterm birth and LBW can be found in the first trimester, we assume that the high rate of preterm births among women exposed to AZA is explained by the underlying maternal disease [14,17,25] and possibly also by exposure to AZA during the first trimester. In one study [16], the rate of preterm births was higher in women treated with AZA (21.4%) than in a control group (5.2%) and the mean weight of the newborn babies was significantly lower in the AZA group (2995 ± 816 g vs. 3252 ± 520 g, respectively). However, when corrected for gestational age, there was no significant difference between the two groups and there was no difference in the average weight of the babies born at term (>37 weeks of gestation). A recent meta-analysis on birth outcomes in women with IBD concluded that thiopurine exposure is associated with preterm birth, but not with LBW or congenital abnormalities [23].

The main strength of the present study is that outcome data were prospective because only requests received before gestational week 22, i.e. before detailed fetal ultrasound, were included. Moreover, to minimize the confounding factor of the underlying condition, we used a control group of women with a similar chronic disease. There were still some significant differences between our two groups. However, the main maternal characteristics were comparable between the two groups, including important confounding or risk factors, such as maternal age and gestational age at call. We acknowledge that data for some important variables such as smoking, and obstetric history are missing and that this lack of data may have interfered with the interpretation of the results. Similarly, missing values complicate the adjustment of outcome parameters and this can influence the analysis of pregnancy outcome in both directions. The median duration of AZA exposure for fetuses exposed during the first trimester only was 8 weeks of gestation; therefore, the risk of birth defects may have been underestimated. In addition, the sample size of 124 pregnancies with only 96 pregnancies evaluable for birth defects is perhaps too small to detect a tripling in the rate of birth defects.

The FDA has given thiopurines a class ''D'' rating, but critical reviews of the safety of AZA during pregnancy [24,43] suggest that AZA is not a human teratogen. Despite its limitations, our study does not support the idea that the use of AZA during pregnancy is associated with a major risk of congenital malformations. Furthermore, we find that exposure to AZA during the third trimester is not associated with a significant increase in LBW or premature birth. Larger studies are needed to confirm these findings.

Disclosure of interest

The authors declare that they have no competing interest.

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