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The effects of azathioprine on birth outcomes in women with inflammatory bowel disease (IBD)

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Abstract

Aim: To investigate the effects of azathioprine/6-mercaptopurine (AZA/6-MP) on birth outcomes in women with inflammatory bowel disease (IBD).
Methods: Details of pregnant women with IBD were obtained through an ObstetriX Database in 3 major teaching hospitals in Sydney from 1996 to 2006. Medical records were reviewed. Birth outcomes of interest were single live births, low birth weight (LBW) at term (<2500 g), preterm births (<37 weeks gestation), neonatal adverse outcomes, and congenital anomaly. Placental blood flow during third trimester of pregnancy was measured using arterial Doppler ultrasonography, where available.
Results: All women had IBD diagnosed before pregnancy. 19 births were exposed to AZA/6-MP. 74 births that were never exposed to AZA/6-MP were selected as controls. Preterm birth was seen in 26.3% of the exposed group as compared to 13.5% of controls ($p<0.001$). However, in univariate analysis, preterm birth was not associated with AZA/6-MP (OR=2.28; CI: 0.67–7.73). There was 1 neonatal adverse outcome in the exposed group as compared to 4 in controls (5.3% vs 5.4%, $p=0.97$). One congenital anomaly was seen in each group ($p=0.27$). No LBW at term was seen in either group. Placental blood flow in 4 women exposed to AZA/6-MP was normal.
Conclusion: The use of AZA/6-MP during pregnancy in IBD women was not associated with an increased risk of preterm birth, LBW at term, neonatal adverse outcomes and congenital anomalies.

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1. Introduction

Inflammatory bowel disease (IBD) is a chronic disorder which commonly affects women of childbearing age. The use of one or more medications is often required to enable adequate control of the disease. Azathioprine (AZA) or 6-mercaptopurine (6-MP) has been shown to be effective in both induction and maintenance of remission in Crohn's disease (CD).[1,2] Its efficacy has also been demonstrated in ulcerative colitis (UC).[3]

There have been concerns regarding the use of AZA/6-MP during pregnancy due to its ability to cross the placenta.[4] Animal studies have suggested its potential teratogenicity, however, information in humans is less clear.[5] In IBD, safety of these immunomodulating agents in pregnant women remains controversial. In a retrospective cohort study, Francella et al.[6] has demonstrated no increase in adverse birth outcomes with the use of 6-MP in women with IBD, whereas a recent population-based study in Denmark[7] showed that the risk of preterm birth was greater in women with CD treated with AZA/6-MP.

Stopping this medication, on the other hand, risks flare of the disease which has been shown to be associated with an increased risk of low birth weight or preterm birth.[8,9] Furthermore, active disease around the time of conception is associated with a high risk of the disease remaining active or deteriorating.[10] As a result, clinicians are often faced with the dilemma of advising their patients to either stop or continue the medication before or during pregnancy.

The aim of this study was, therefore, to determine the effects of AZA/6-MP on birth outcomes in pregnant women with IBD in an Australian population.

2. Materials and methods

All women with IBD (UC or CD) who were pregnant between 1996 and 2006 were included in this case–control study. These women were identified through an ObstetriX Database from 3 major teaching hospitals (Nepean Hospital, Westmead Hospital, and Royal North Shore Hospital) in Sydney, Australia. Medical records of eligible women were reviewed. Their age, parity, self-reported smoking and alcohol history, diagnosis of IBD, medications used before and during pregnancy, and mode of delivery were recorded. Where available, hospital admissions during pregnancy due to a flare of the disease were used as a surrogate marker for disease activity. Birth outcomes of interest were single live births, low birth weight (LBW) at term (<2500 g), preterm births (<37 weeks gestation), congenital anomalies, and neonatal adverse outcomes (defined as outcomes necessitating admission to neonatal intensive care unit). In one of the centers (Nepean Hospital), placental blood flow during the third trimester of pregnancy was measured by a perinatologist (H.M) using arterial Doppler ultrasonography. Where available, this information was recorded. As it was not possible to accurately document whether AZA/6-MP was stopped around the time of conception, only births from women with IBD who reported taking these medications during their first antenatal visit (i.e. first trimester) were identified as the exposed group. Births from age-matched women with IBD who were not exposed to AZA/6-MP before and during their pregnancy were selected as controls. The study protocol was approved by the Human Research Ethics Committee of Sydney West Area Health Service and Royal North Shore Hospital.

2.1. Statistical analysis

Differences in mean scores were determined using a *t*-test. Patient demographic and clinical characteristics have been reported as mean and standard deviation for numeric-scaled features and percentages for discrete characteristics. Risk factors for preterm birth were identified using unconditional logistic regression. Analysis proceeded in two steps, i) identification of statistically significant univariate risk factors and ii) inclusion of the univariate significant risk factors in a multiple logistic regression model. This two step process provides a complete risk factor profile for preterm birth. Model identification employed a forward stepwise procedure using odds ratios (OR) and 95% confidence intervals (CI). All p-values calculated were two-tailed; the alpha level of significance was set at 0.05.

3. Results

93 births from 63 women were eligible in the study. Of these, 19 births were identified as the exposed group. The remaining 74 births comprised as controls. No spontaneous abortions were identified in both groups. All mothers in the exposed group were taking AZA/6-MP throughout the duration of their pregnancy.

3.1. Characteristics

The characteristics of women with IBD who were exposed to AZA/6-MP compared to those who were not exposed to the medications are shown in Table 1. There was no difference in mean age between the exposed group and controls. Of the 19 births, only 1 was exposed to 6-MP (100 mg) during pregnancy. The remaining 18 were receiving AZA at an average dose of 100 mg (range 50–200 mg). Smoking during pregnancy was more common in women who were exposed to AZA/6-MP, whereas, alcohol consumption was more common in the control group. During pregnancy, more women who were exposed to AZA/6-MP were treated with 5-aminosalicylic acid (5-ASA) and corticosteroids. None of the women in either group were treated with methotrexate, cyclosporine, ciprofloxacin, or biologic therapy. The exposed group also had more hospitalization for a flare of their disease during pregnancy compared to controls. With regard to mode of delivery, there were more vaginal deliveries in both groups as compared to cesarian sections, and vaginal delivery was more prevalent in women who were exposed to AZA/6-MP than controls.

3.2. Birth outcomes

Results of birth outcomes in women with IBD who were and were not exposed to AZA/6-MP are shown in Table 2. Gestational age tended to be lower in the exposed group (37.8±0.6 weeks vs 39.2±0.3 weeks, p=0.06). Preterm births were seen in 26.3% of women exposed to AZA/6-MP and 13.5%

Table 1 Characteristics of women with inflammatory bowel disease (IBD) who were and were not exposed to azathioprine/6-mercaptopurine (AZA/6-MP) during pregnancy.

	Exposed (n=19)	Controls (n=74)	p value
Maternal age (mean years ± SE)	28.8 ± 0.8	30.8 ± 0.6	NS
Parity (≥1)	11 (57.9)	41 (55.4)	NS
IBD subtypes			
CD	15 (78.9)	55 (74.3)	NS
UC	4 (21.1)	19 (25.7)	NS
Smoking [a]	7 (36.8)	11 (14.9)	<0.001
Alcohol consumption [a]	0	4 (5%)	<0.001
Azathioprine [a]	18	0	
6-MP [a]	1	0	
5-ASA [a]	13 (68.4)	34 (45.9)	<0.001
Corticosteroids [a]	11 (57.9)	9 (12.2)	<0.001
Hospitalization for flare of disease [a]	6 (31.6)	9 (12.2)	<0.001
Mode of delivery			
Cesarian section	4 (21.1)	30 (40.5)	<0.001
Vaginal delivery	15 (78.9)	44 (59.5)	<0.001

Percentages in parentheses.
NS — non significant.
[a] During pregnancy.

in controls ($p<0.001$). There was 1/19 neonatal adverse outcome in women exposed to AZA/6-MP as compared to 4/74 in the control group. All the adverse outcomes required admission to neonatal intensive care unit due to respiratory distress. In the exposed group, the infant was a preterm baby born at 32.6 weeks with a gestational weight of 1649 g. The infant's mother had UC and was taking a 5-ASA agent and oral corticosteroids in addition to AZA during the pregnancy. She did not report smoking or any alcohol consumption during her pregnancy, and had not had any hospitalization due to a flare of her disease throughout her pregnancy. The infant was discharged from the intensive care unit with no associated short-term morbidity.

Table 2 Birth outcomes of women with inflammatory bowel disease (IBD) who were and were not exposed to azathioprine/6-mercaptopurine (AZA/6-MP) during pregnancy.

	Exposed (n=19)	Controls (n=74)	p value
Birth weight (g)	3022 ± 147	3283 ± 89	NS
Gestational age (weeks)	37.8 ± 0.6	39.2 ± 0.3	NS
Preterm birth (<37 weeks gestation)	5 (26.3)	10 (13.5)	<0.001
Low birth weight at term (<2500 g)	0	0	
Neonatal adverse outcomes [a]	1 (5.3)	4 (5.4)	NS
Congenital anomalies	1 (5.3)	1 (1.4)	NS

Birth weight and gestational age expressed as mean ± SE; percentages in parentheses.
NS — non significant.
[a] Defined as outcomes necessitating admission to neonatal intensive care unit.

One congenital anomaly was seen in each group. In the group exposed to AZA/6-MP, the infant was a term baby born with a congenital hyperplastic heart. The infant's mother had CD and was only taking AZA throughout her pregnancy. She was a non-smoker and did not consume alcohol beverages during pregnancy, and had no hospitalization due to a flare of her disease throughout her pregnancy. The other infant was also a term baby born to a mother with CD who was not on any medication during her pregnancy. This infant had congenital reflux nephropathy.

3.3. Relative risks of adverse birth outcomes

In univariate analysis, AZA/6-MP use was significantly associated with smoking (OR = 3.34; CI: 1.08–10.35) and corticosteroids use (OR = 9.93; CI: 3.15–31.26) (Table 3). In a multivariate analysis, only corticosteroids use (OR = 8.80; CI: 2.73–28.30) was independently associated with adverse birth outcomes. None of the adverse birth outcomes were associated with AZA/6-MP.

3.4. Placental blood flow measure

Placental blood flow during the third trimester of pregnancy was measured using arterial Doppler ultrasonography in 4 women who were exposed to AZA/6-MP. Three of the women were taking 150 mg of AZA and one took 100 mg of AZA. All women were exposed to AZA throughout the pregnancy. The

Table 3 Univariate and multivariate analysis associated with use of azathioprine/6-mercaptopurine (AZA/6-MP) in women with inflammatory bowel disease (IBD) during pregnancy.

	Univariate odds ratio, 95% CI	Adjusted odds ratio, 95% CI
Maternal age	0.92 (0.83–1.03)	
Parity	1.26 (0.80–1.99)	
Smoking	3.34 (1.08–10.35)	2.41 (0.67–8.66)
Mode of delivery	0.77 (0.23–2.61)	
Corticosteroids	9.93 (3.15–31.26)	8.80 (2.73–28.30)
5-ASA	2.54 (0.87–7.43)	
Hospitalization [a]	1.26 (0.23–6.85)	
Gestational age (weeks)	0.86 (0.72–1.01)	
Low birth weight at term (<2500 g)	1.00 (0.99–1.01)	
Preterm birth (<37 weeks gestation)	2.28 (0.67–7.73)	
Neonatal adverse outcomes [b]	0.97 (0.10–9.23)	
Congenital anomalies	4.05 (0.24–67.99)	

[a] Hospitalization for a flare of disease is used as surrogate marker for disease activity.
[b] Defined as outcomes necessitating admission to neonatal intensive care unit.

results of placental blood flow were all normal, and there were no adverse birth outcomes for all the 4 women.

4. Discussion

This study showed that there was no increased risk of preterm birth, LBW at term, neonatal adverse outcomes, and congenital anomalies in pregnant women with IBD who were exposed to AZA/6-MP. To our knowledge, this is the first Australian study examining the effects of AZA/6-MP on birth outcomes in women with IBD. The findings are important as a flare of the disease during pregnancy has been shown to be associated with adverse birth outcomes.[8,9] A case–control study of 18 IBD patients with severe relapses whilst pregnant was associated with an increased incidence of LBW and preterm births when compared to pregnant IBD patients without disease relapse.[8] This has important implications as LBW and preterm infants are associated with high morbidity and mortality rates.[11,12] Hence, in IBD women who require AZA/6-MP for disease control, strong consideration should be made for continuation of the treatment during pregnancy.

Our findings are comparable with other studies which have similarly examined the use of AZA/6-MP in IBD women during pregnancy.[6,13,14] In a retrospective cohort study by Francella et al.[6], there was no reported increase in prematurity, spontaneous abortion, congenital anomalies, or neonatal and childhood infections in patients who were exposed to 6-MP prior to and during pregnancy when compared with controls. In another study,[14] there was also no significant increase in adverse birth outcomes in IBD women exposed to AZA/6-MP. However, a recent population-based study in Denmark[7] found that in CD women who were exposed to AZA/6-MP during pregnancy, the adjusted relative risk of preterm birth was 4.2 (95% CI: 1.4 to 12.5). Similarly in another study[15] examining 76 pregnancies exposed to AZA/6-MP (of which 54% women had IBD), the authors found an increased risk of preterm birth and congenital anomaly when compared to unexposed controls. However in that study,[15] when comparisons were limited to women who had similar underlying diseases as the exposed group, the relative risk of preterm birth was only increased for induced, but not spontaneous delivery, and risk of congenital anomaly was no longer significant.

In our cohort, the overall mean maternal age was 31 years which was similar to other studies.[7,14] There was a higher proportion (36.8%) of women in our exposed group who reported smoking whilst pregnant when compared to controls. This is consistent with a recent study[7] of which 45% of pregnant women with CD who were taking AZA/6-MP were smoking. As patients with CD who smoke are more likely to have active disease,[16] it is possible that these women are therefore more likely to be treated with AZA/6-MP.

Our study showed that women who were taking AZA/6-MP were 8 times more likely to be treated with corticosteroids. This is not unexpected as patients who require the use of AZA/6-MP as maintenance therapy will often be treated with corticosteroids for inducing remission. 50% of our exposed group was concurrently treated with oral corticosteroids, however only about a third of them were hospitalized for a flare of their disease during pregnancy. This highlights that the exposed group may have mild–moderate disease of which an out-of-hospital management with oral corticosteroids were sufficient to control flares of their disease. Nevertheless, after adjusting for corticosteroids use and disease activity, we found no increased risk with adverse birth outcomes in women treated with AZA/6-MP.

Overall, there were a higher number of women with IBD who had vaginal deliveries than cesarian sections in our study. This is in contrast to a recent meta-analysis[17] which showed that IBD patients are 1.5 times more likely to have cesarian sections than controls. It was uncertain whether the higher incidence of cesarian sections was due to electives or emergencies. Women with IBD can generally have vaginal delivery except for those with CD who have active perianal disease due to possible risk of exacerbations.[18] As a detailed history of the extent of IBD was not uniformly available from the medical files, we were unable to know the proportion of women with perianal disease in this cohort.

The most feared birth outcome by pregnant women with IBD is risk of a congenital malformation. It remains controversial whether IBD increases risk of congenital anomaly. A number of studies[6,19] have shown that the risk of congenital anomaly in IBD patients was no different to the 2–4% reported incidence in the general population.[20] However, a study by Dominitz et al.[21] showed that patients with UC have an increased incidence of congenital anomaly vs controls (OR 3.8; 95% CI 1.5 to 9.8), but not in patients with CD. Overall, our patients had a 2.1% risk of congenital anomaly which is in accord with the general population.[20] In addition, we found that AZA/6-MP was not associated with an increased risk of congenital anomaly in IBD women, which is supported by other studies.[6,7,15]

Abnormal blood flow of the umbilical artery has been associated with increased perinatal morbidity and mortality.[22] Doppler ultrasound studies used in assessing fetal–placental circulation in high risk pregnancies such as pre-eclampsia has been shown to predict fetal well-being and outcome of pregnancy.[23] However, its use in patients with IBD is virtually non-existent. We have measured the placental blood flow in 4 IBD women who were on AZA/6-MP. They were all normal. Further studies will be needed in this area to establish its role in IBD pregnancy.

The main strength of our study is the use of a standardized Obstetrics Database which minimizes recall bias. We recorded data over a 10 year period and included all women with IBD. We also examined placental blood flow which is a novel aspect of this study.

We also acknowledge some limitations in this study. The sample size in the exposed group was small despite including patients from three large teaching hospitals. There was a lack of adequate documentation regarding the use of AZA/6-MP around the time of conception, hence we may have potentially underestimated the actual number of patients who were exposed to the medications. We were also unable to obtain an adequate history of the disease from the medical files, hence the extent of disease activity and IBD related surgeries was uncertain.

In conclusion, our study showed that there was no increased risk with preterm birth, LBW at term, neonatal adverse outcomes, and congenital anomaly in women with IBD exposed to AZA/6-MP. Therefore, consideration should be made for continuation of these medications during pregnancy as a flare of the disease can result in adverse birth outcomes.

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