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Short Report

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Successful Pregnancies with Thiopurine-Allopurinol Co-Therapy for Inflammatory Bowel Disease

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Abstract

Background: Thiopurines are an effective treatment for moderate to severe inflammatory bowel disease [IBD] and can be used safely in pregnancy. Combining allopurinol with a lower dose of thiopurine can improve clinical efficacy and bypass some adverse reactions associated with thiopurine monotherapy. Data on allopurinol in pregnancy are scarce. We report on a total of 13 cases where thiopurine and allopurinol co-therapy was used successfully to manage IBD during pregnancy without attributable adverse fetal effects.
Methods: Patients were retrospectively identified at our two hospitals, one in the UK and one in Australia, using local IBD databases. Data regarding pregnancy and fetal outcomes including *in utero* fetal ultrasound scans, APGAR scores, fetal birthweights and neonate checks were collected from patient notes.
Results: We identified 12 women with a total of 13 pregnancies treated with co-therapy before conception and for the duration of pregnancy. There were no miscarriages or spontaneous pre-term deliveries. There were 14 live births [seven vaginal deliveries; six caesarean sections]. Except for a primagravid twin pregnancy complicated by pre-eclampsia and twin-to-twin transfusion syndrome requiring caesarean section at 25 weeks, there were no low birthweight [< 2.5 kg] babies born and the APGAR scores of all babies were normal. No congenital malformations were identified.
Conclusions: Adverse pregnancy outcomes attributable to thiopurine and allopurinol co-therapy were not detected in our case series. Our study provides reassurance for clinicians and patients who wish to continue the thiopurine-allopurinol co-therapy combination before conception and during pregnancy to maintain remission of IBD.

Keywords: Thiopurine; allopurinol; pregnancy

1. Introduction

Inflammatory bowel disease [IBD] affects many women of child-bearing age. Thiopurines (azathioprine[AZA] and mercaptopurine [6MP]) are an effective oral treatment for moderate to severe IBD. There is considerable evidence to support their safety in pregnancy without adverse fetal effects[1] such as low birthweight or congenital abnormalities.[2] There is a strong medical consensus that advocates

the importance of maintaining disease remission before conception and during pregnancy[3] because disease flares are the main predictor of adverse pregnancy outcomes.[4] The combination of allopurinol with a lower dose of AZA or 6MP has been recently shown to circumvent some adverse drug reactions associated with thiopurines and improve efficacy of thiopurine monotherapy.[5,6]

Allopurinol is classed by regulatory bodies such as the Therapeutic Goods Association of Australia, or the US Food and Drug Administration [FDA], as a category C drug in pregnancy. However there are few data concerning allopurinol and pregnancy because few women of childbearing age require allopurinol therapy. Animal studies with allopurinol have demonstrated evidence of teratogenicity at high doses in mice[7] but not in rats.[8] There are only four reported cases of the combined use of thiopurine and allopurinol during pregnancy: one case report,[9] where 6MP was used in conjunction with allopurinol to successfully treat ulcerative colitis [UC], and a series of three cases of co-therapy from Australia.[10] No adverse fetal outcomes were reported for any of the four pregnancies.

We report a total of 13 cases from two centres in the UK and one in Australia, where thiopurine and allopurinol co-therapy was used successfully to manage IBD from before conception and throughout the duration of pregnancy. This represents the largest case series of thiopurine and allopurinol co-therapy for IBD in pregnancy to date.

2. Case Report

Patients were retrospectively identified at East Surrey Hospital, UK, and the Mater Health Services' Hospital in Brisbane, Australia, using our local electronic IBD databases. We identified patients from January 2010 to September 2013, treated with thiopurine and allopurinol, who became pregnant. All pregnancies of co-therapy patients were included. All female patients before commencing co-therapy treatment were counselled about possible adverse reactions of medication and risks in pregnancy. Those considering pregnancy had additional consultations before conception to further discuss risks and benefits. Thiopurine S-methyltransferase [TPMT] activity and pre-pregnancy weight were used to calculate thiopurine dosing, which was reduced to one-third following addition of allopurinol as per Ansari *et al*.[11]

Patients were followed during their pregnancies in outpatient gastroenterology and obstetric clinics. IBD clinical activity was measured using clinical parameters—the simple clinical colitis score for UC and the Harvey Bradshaw Index for Crohn's disease [CD] activity—at clinic visits. In addition we performed routine blood tests including haematology, biochemistry, liver function, and CRP. Fetal ultrasound scans were performed at 12, 22, and 28 weeks for all patients in the UK centre, and according to routine clinical practice in Australia. At birth, APGAR scores were calculated at 1 and 5 min, birthweights were measured and neonate checks were performed by a paediatrician as routine practice for medically complex cases. Data regarding pregnancy and fetal/neonatal outcomes were collected retrospectively from patient notes. Postnatally women were contacted to ask about any neonatal complications including vaccination status.

We identified 12 females [9 UC, 3 CD] on co-therapy who became pregnant, with a total of 13 pregnancies during the study period [Table1]. All patients had been receiving thiopurine-allopurinol co-treatment as part of their ongoing disease management and then continued treatment through pregnancy. Mean daily doses of thiopurine and allopurinol were AZA 41 mg [n = 4], 6MP 31mg [n = 9], and allopurinol 108 mg. The median duration of co-therapy before successful conception was 12 months, [range 1–72 months]. All patients demonstrated a good treatment response with co-therapy based on clinical grounds, as evidenced by improvements in the simple clinical colitis score for UC and the Harvey Bradshaw Index for CD activity, with disease activity largely in remission or only mild at time of conception.

There were 14 live births, as one pregnancy [case 13] resulted in twins. One patient became pregnant twice [first pregnancy Case 5 and second pregnancy Case 12]; both of her pregnancies were achieved with *in vitro* fertilisation. For all pregnancies except one [Case 4], drug doses were maintained the same as those before conception. Case 4 had been receiving AZA 50 mg and allopurinol 100 mg but developed hepatotoxicity as evidenced by a rise in alanine aminotransferase [ALT]; this resolved on increasing the allopurinol dose to 200 mg. Co-therapy was well tolerated in pregnancy, with only one patient [Case 10] stopping allopurinol at 6 months due to nausea. Medications taken during pregnancy are listed in Table 1. All patients took folic acid supplementation.

Median age at pregnancy was 31 years, range 21 to 36. There were no reported miscarriages or terminations. There was only one disease flare during pregnancy [Case 2], which occurred at 30 weeks, was mild, and was treated successfully with mesalazine enemas. No fetal abnormalities were noted *in utero* on ultrasound scan examinations except for Case 13, which was a primagravid twin pregnancy complicated by pre-eclampsia and twin-to-twin transfusion syndrome [TTTS]. There were no spontaneous pre-term deliveries [i.e. < 37 weeks]. Seven patients gave birth by spontaneous vaginal delivery [SVD] and six by caesarean section [C-section] [Cases 2, 3, 7, 8, 11, and 13]. One patient [Case 7] had a C-section at 36 weeks. She had cervical incompetence and insertion of a cervical suture. This patient [with UC] had previously suffered a miscarriage of twins at 24 weeks, which occurred during a severe disease flare, before the commencement of co-therapy. She was also taking liposomal cyclosporine throughout her pregnancy. Case 2 required an emergency C-section for failure to progress in labour and Case 3 because of a previous C-section. Elective C-sections were performed for Cases 8 and 11. Case 13, who underwent a C-section at 25 weeks for pre-eclampsia and TTTS, delivered two live babies weighing less than 400 g. One twin did not survive beyond 13 weeks post delivery due to respiratory failure and an intracerebral bleed; the other twin was doing well at 16 weeks.

Except for Case 13 there were no low birthweight babies [< 2.5 kg] and the APGAR scores of all babies were normal at 1 and 5 min. Subsequent routine neonate checks identified no evidence of congenital malformations, other medical abnormalities or infectious complications. The median duration of follow-up of babies was 6 months. There has been no indication of any morbidity such as failure to thrive during the follow-up period. Vaccination of neonates has occurred in accordance with standard national protocols with no evidence of any infectious complications.

3. Discussion

All 12 IBD patients were treated successfully with thiopurine and allopurinol before and during their pregnancies. There were no adverse pregnancy-related events or adverse fetal or neonatal outcomes with the exception of Case 13, who had pre-eclampsia and TTTS. TTTS complicates approximately 10% of monochorionic diamniotic pregnancies and is a consequence of intertwin vascular connections within the placenta leading to an imbalance of blood flow.[12] It is not known to be related to maternal drug treatment. Pre-eclampsia affects 3–5% of pregnancies, is more common in multiple and primiparous

Table 1 A

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Diagnosis	**UC**	**UC**	**UC**	**UC**	**UC**	**UC**
Pregnancies prior to co-therapy	Nil	Nil	One; healthy neonate	Nil	Nil	Two; 1st, miscarriage due to flare; 2nd, neonate with cataracts
Dose thiopurine/allopurinol	AZA 50 mg, Allo 100 mg 7 d/wk	AZA 25 mg 5 d/wk, 50 mg 2 d/wk Allo 100 mg	AZA 25mg 5 d/wk, 50 mg 2 d/wk, Allo100 mg	AZA 50 mg, Allo 200 mg 7 d/wk	6MP 50 mg + Allo 100 mg, 5 d/wk	6MP 50 mg + Allo 100 mg, 5 d/wk
Duration of pre-pregnancy co-therapy [months]	6	19	1	12	14	6
Disease severity pre- co-therapy	Moderate	Severe	Mild	Moderate	Moderate	Moderate
Disease severity pre-conception	Clinical remission	Mild	Clinical remission	Clinical remission	Clinical remission	Clinical remission
Age at pregnancy [years]	21	24	34	31	30	36
Other medication during pregnancy	Omeprazole, Pentasa, Ferrous fumarate, Adcal	Pentasa		Ferrous fumarate	Balsalazide	Mesalazine
Number of flares in pregnancy	0	1	0	0	0	0
Abnormalities on fetal ultra-sounds	None	None	None	None	None	None
Gestation at delivery [weeks]	41	38	39	40	38	39
Mode of delivery	SVD	C-section	C-section	SVD	SVD	SVD
Fetal birthweight [kg]	3.5	2.9	3.4	4.0	3.8	3.0
APGAR scores at 1 and 5 min	Normal	Normal	Normal	Normal	Normal	Normal
Neonate check	Normal	Normal	Normal	Normal	Normal	Normal

B. Pregnancy and fetal outcomes with thiopurine and allopurinol co-therapy

	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13
Diagnosis	**UC**	**CD**	**CD**	**CD**	**UC**	**UC**	**UC**
Pregnancies prior to co-therapy	One; miscarried due to flare	Nil	Nil	One; healthy neonate	Nil	Nil	Nil
Dose thiopurine/allo-purinol	6MP 25 mg + Allo 100 mg, 3 d/wk	6MP 50 mg + Allo 100 mg, 6 d/wk	6MP 50 mg + Allo 100 mg, 4 d/wk	6MP 50 mg + Allo 100 mg, 4 d/wk	6MP 50 mg + Allo 100 mg, 5 d/wk	6MP 50 mg + Allo 100 mg, 5 d/wk	6MP 50 mg + Allo 100 mg, 4 d/wk
Duration of pre-pregnancy co-therapy [months]	15	24	7	2	5	38	72
Disease severity pre- co-therapy	Severe	Moderate	Quiescent [perianal disease]	Moderate	Moderate	Moderate	Moderate
Disease severity pre-conception	Clinical remission	Mild	Clinical remission	Mild	Clinical remission	Clinical remission	Mild
Age at pregnancy [years]	32	29	34	29	32	32	31
Other medication during pregnancy	Ciclosporin, ferrous fumarate	Ferrous fumarate	Adalumin-ab, ferrous fumarate	Allopurin-ol stopped at 6 months	Ferrous fumarate	Balsala-zide	Mesalazine
Number of flares in pregnancy	0	0	0	0	0	0	0
Abnormalities on fetal ultrasounds	None	None	None	None	None	None	TTTS
Gestation at delivery [weeks]	36	38	38	38	38	39	25
Mode of delivery	C-section	C-section	SVD	SVD	C-section	SVD	C-section
Fetal birthweight [kg]	2.9	3.5	3.4	3.1	3.1	3.8	Twins < 0.4
APGAR scores at 1 and 5 min	Normal	Normal	Normal	Normal	Normal	Normal	-
Neonate check	Normal	Normal	Normal	Normal	Normal	Normal	Twin 2 died at 13 wks, twin 1 normal at 16 wks post-delivery

UC, ulcerative colitis; CD, Crohn's disease; AZA, azathioprine; allo, allopurinol; d, day; wk, week; 6MP, 6-mercaptopurine; C-section, caesarean sction; SVD , spontaneous vaginal delivery; TTTS, twin-to twin transfusion syndrome.

pregnancies, and is not thought to be related to thiopurine therapy.[13] Although we did not measure thiopurine metabolite levels, intrauterine exposure of the fetus to thiopurine metabolites [6-TGN and 6-MMP] is not greater with combination therapy compared with thiopurine monotherapy.[9] Allopurinol and its metabolite oxypurinol have been shown to cross the placenta following a single dose of maternal allopurinol but at levels lower than maternal plasma levels.[14]

A large prospective case series [n = 31] of maternal use of allopurinol during pregnancy for primary and secondary hyperuricaemia was recently published.[15] It reported that the rates of congenital malformations and spontaneous miscarriages were in the expected range, as were birthweights. However the prematurity rate of 19% was high, which the authors ascribed to the serious underlying disease comorbidity rather than allopurinol use. One child was born with serious congenital malformations, which appeared to be phenotypically similar to the only case report suggesing a potential teratogenic effect of allopurinol.[16] However, the case for an association based on the two cases is weak. Moreover we suspect there is also likely to be a negative publication bias with respect to allopurinol use and successful pregnancy outcomes, given the scarcity of allopurinol-related pregnancy data over the five decades for which allopurinol has been used. On the other hand, use of maternal allopurinol at the time of birth could protect the fetus against the effects of hypoxia.[14]

A limitation of this retrospective case series is the relatively small number of patients, so the probability of detecting an uncommon congenital malformation is unlikely. Although comprising only 13 pregnancies, the series is the largest reported to date.

In conclusion, adverse pregnancy-related events attributable to combination thiopurine and allopurinol therapy for IBD were not detected. Importantly, it is of clinical significance that co-therapy was efficacious in maintaining disease remission during pregnancy, because disease flares are the main prognosticator for poor pregnancy outcomes.

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MS, TF, and AA were responsible for study concept and design and acquisition of data. All authors were involved in analysis and interpretation of data, writing and critical revision of the manuscript. All authors approved the final manuscript.

Conflict of Interest

The authors have no conflicts of interest to declare.

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