Aliment Pharmacol Ther 1998; 12: 1101–1108.

Foetal outcome in women with inflammatory bowel disease treated during pregnancy with oral mesalazine microgranules

P. MARTEAU*, R. TENNENBAUM†, E. ELEFANT‡, M. LÉMANN§ & J. COSNES†

**Service d'Hépato-gastroentérologie, Hôpital Laënnec and Hôpital Saint-Lazare, Paris, France; †Service d'Hépato-gastroentérologie, Hôpital Rothschild, Paris, France; ‡Centre de Renseignement sur les Agents Tératogènes, Hôpital Saint-Antoine, Paris, France; and §Service d'Hépato-gastroentérologie, Hôpital Saint-Louis, Paris, France*

Accepted for publication 15 July 1998

SUMMARY

Background: Little information is available about the safety of high doses of mesalazine during pregnancy.

Aim: To study the fate of pregnancy and foetal outcome in women taking 1–4 g/day of mesalazine microgranules for inflammatory bowel disease.

Patients and methods: Case reports were collected from the Pharmacovigilance Department of Ferring SA, France, from a survey conducted in three gastroenterology units, and from a teratology information service. The evolution of pregnancy and foetal outcome were assessed by questionnaire.

Results: The study covered a total of 123 pregnancies (126 foetuses). Ninety-six women took mesalazine during the first trimester, 85 during the second and 83 during the third. The mean daily dose was 2.1 ± 0.8 g; 86 women received <3 g/day (low-dose group), 37 women received ≥3 g/day (high-dose group). The following abnormalities were observed in the low-dose and high-dose groups, respectively: ectopic pregnancy (1/0), spontaneous abortions (1/1), foetal death (0/1), premature deliveries (3/5, $P < 0.05$), congenital malformations (3/1) and one case of lethal oxalosis. Abnormalities were not considered to be related to mesalazine.

Conclusions: The use of oral mesalazine microgranules during pregnancy is safe at doses ≤ 2 g/day, and probably also at a dose of 3 g/day.

INTRODUCTION

Many women with inflammatory bowel disease are of reproductive age. Epidemiological studies have shown that inflammatory bowel disease is associated with a significant risk of increased premature delivery.[1–8] The risks of foetal loss and of malformations are usually in the normal range, i.e. 1–2% and 1.7–3.4%, respectively.[1–11] However, both were found to be significantly higher than in the general population in a recent Italian study.[12] Nearly all the drugs used to treat inflammatory bowel disease, i.e. corticosteroids, azathioprine, methotrexate, metronidazole and 5-aminosalicylic acid (5-ASA), cross the placenta.[13–15] Of these, corticosteroids can be used safely.[1–4, 16, 17] In a retrospective study of 16 pregnancies, Alstead *et al.*[18] suggested that azathioprine was also safe in pregnant women with inflammatory bowel disease, as it is in pregnant women undergoing renal transplantation or suffering from lupus erythematosus.[19–21] Methotrexate is a folic acid antagonist which is teratogenic in animals; its use is therefore contraindicated in pregnant women.[22] Metronidazole is foetotoxic, teratogenic and carcinogenic in mice, but does not appear to be associated with an increased teratogenic risk in humans.[23] Isolated reports of congenital malformations have raised the question of the potential teratogenicity of sulphasalazine.[24–26] However, studies of several large series of inflammatory

Correspondence to: Prof. P. Marteau, Hôpital Laënnec, 42 rue de Sèvres, 75007 Paris, France.
E-mail: philippe.marteau@lnc.ap-hop-paris.fr

bowel disease patients showed that it did not increase the risk of newborn abnormalities.[4, 16] When new 5-ASA derivatives were developed, it was postulated on the basis of their pharmacokinetics and especially of their peak serum concentration, that certain oral formulations such as Pentasa mesalazine microgranules or Asacol could probably be used safely, but that more information was needed on the safety of formulations with higher serum peak levels, such as Salofalk and Claversal.[14] The outcome for three small series of 11, 17 and 19 pregnancies indeed suggested that Asacol[27, 28] and Pentasa[29] at doses below 2.4 g/day appeared to be safe during pregnancy. However, Colombel *et al.* reported a case of renal disease in a newborn infant whose mother received 4 g/day Pentasa during pregnancy;[30] no information was available at that time in the literature about the safety of doses above 3 g/day.

We therefore decided to study the outcome of pregnancy in a large number of women receiving Pentasa during pregnancy, especially in women given high doses.

SUBJECTS AND METHODS

Surveys

We collected information on the outcome of pregnancy in women treated with Pentasa (Ferring SA, Copenhagen, Denmark) in France between September 1989 and January 1996. Cases were obtained from three sources: (i) a survey by the Pharmacovigilance Department of Ferring SA, France, (ii) a retrospective study conducted in three gastroenterology units in Paris specializing in the treatment of inflammatory bowel disease, and (iii) a prospective survey by the Teratogen Information Service, Saint-Antoine Hospital. During the period of the study, two articles were published which reported the outcome of pregnancy for 12 women given Pentasa in France during pregnancy.[25, 26] These findings are not included in the Results section of this paper but are summarized in the Discussion.

Ferring Pharmacovigilance Department. Cases were reported to the Pharmacovigilance Department either by Regional Drug Monitoring Centres or directly by practitioners. As soon as a physician reported a case or asked for information, the legal contraindication concerning the use of Pentasa during pregnancy at the time of the study in France was recalled by a phone call and by mail, and a questionnaire on the fate of pregnancy and foetal outcome was also mailed. As from the date of publication of the case reports on the fate of pregnancy in women given Pentasa,[25, 26] information concerning these cases was sent to the physician together with the questionnaire. Cases reported at the beginning of pregnancy were followed prospectively; the others were assessed retrospectively. Physicians who did not return the questionnaires were contacted again, to obtain the desired information.

Survey in gastroenterology units and by the Teratogen Information Service (T.I.S.). A retrospective survey was conducted in the gastroenterology units of the Rothschild, Saint-Louis and Saint-Lazare hospitals. For this purpose, a questionnaire was sent to all the women of child-bearing age in these units who were being followed for inflammatory bowel disease. The T.I.S. specializes in drug toxicity during pregnancy. When its specialists are contacted by practitioners, a personal file is set up, which includes the patient's initials, age, date of the beginning of pregnancy, medical history, and list of drugs being taken. A questionnaire is then sent by the centre to the practitioner 1 month after the expected term of pregnancy. If the practitioner does not return the questionnaire, another questionnaire is sent 3 months later, and another 1 year later.

Assessment of the fate of pregnancy

The evolution of pregnancy and foetal outcome were assessed by means of questionnaires. The information recorded comprised the patients' initials, date of birth, medical history, chronology and doses of mesalazine ingested, other medications used (with their dose and chronology), follow-up of pregnancy and notification of adverse events concerning pregnancy, delivery and the new-born. Patients' initials and date of birth were used to ensure that patients were not counted more than once.

Groups and statistical analyses

Results are expressed as means ± s.d. The women were separated into two groups according to the maximum daily dose of mesalazine: the low-dose group included women receiving daily doses <3 g/day, and the high-dose group, women who received doses ≥ 3 g/day at any time during pregnancy. Comparisons between groups were made using the chi-squared test for categoric variables, and the Wilcoxon signed rank test for continuous data.

Table 1. Dosage and chronology of Pentasa mesalazine microgranules ingestion by pregnant women (means ± s.d.)*

Origin	F.P.	F.R.	G.U.	T.I.S.
Age (years)	27 ± 4	27 ± 4	30 ± 5	28 ± 4
1st trimester				
No. of women exposed	24	38	18	16
Dose of mesalazine (g/day)	2.0 ± 0.5	2.2 ± 0.8	2.4 ± 0.7	2.2 ± 0.9
2nd trimester				
No. of women exposed	19	37	17	12
Dose of mesalazine (g/day)	1.9 ± 0.4	2.3 ± 0.9	2.2 ± 0.8	2.3 ± 1.1
3rd trimester				
No. of women exposed	20	34	20	9
Dose of mesalazine (g/day)	1.8 ± 0.4	2.3 ± 0.9	2.3 ± 0.8	2.4 ± 1.1

F.P., Ferring prospective study; F.R., Ferring retrospective study; G.U., gastroenterology units; T.I.S., Teratogen Information Service.
*Information on the dosage and chronology was obtained for 109 women.

RESULTS

Population, and dose and chronology of mesalazine ingestion

In total the study covered 123 pregnancies comprising 126 foetuses (three pregnancies were twin).

Eighty-eight of these pregnancies (two of them twin) in women given oral Pentasa for inflammatory bowel disease, were reported to the French Drug Monitoring Centre of Ferring SA. Twelve of them were excluded from this report as they had been included in previous publications.[25, 26] The remaining 76 cases were included. Of these, 62 were fully documented, whereas for 14 (one with a reported adverse event, i.e. oxalosis, and 13 without) the dosage and chronology of Pentasa were not mentioned. Twenty-six of the 76 cases were followed prospectively, and the other 50 were studied retrospectively.

The questionnaire was sent to 828 women fulfilling the selection criteria for the survey in the gastroenterology units. Of these, 520 replied (63%). Twenty-eight of them had received Pentasa orally during pregnancy and were included in this survey; 26 were fully documented, but for the two others (without any reported adverse event) the dosage and chronology were not mentioned.

Nineteen cases of pregnancy (one of them twin) were collected from the T.I.S., and included in the population studied.

The characteristics of the 123 women who fulfilled the study criteria, and the mean dose of Pentasa ingested by each group and its chronology are shown in Table 1. The mean age of the subjects was 28 ± 4 years. The dose and chronology of mesalazine consumption were obtained for 109 women (89%). The daily dose calculated for these 109 cases was 2.1 ± 0.8 g. Thirty-seven women took ≥3 g/day mesalazine (high-dose group). Three took 4 g/day throughout pregnancy, six during the second trimester, and six during the third (Table 2). Seventeen women took 3 g/day throughout pregnancy, 29 during the first trimester, 19 during the second, and 20 during the third (Table 2). Subjects from both groups did not differ in age (28 ± 4 years vs. 30 ± 4 years).

Outcome of pregnancy

One hundred and three babies were born at term, without abnormalities, and did not suffer from postnatal distress (84%). Details concerning the fate of pregnancy in women of the high-dose group are shown in Table 2. Details of the cases in which adverse events occurred during pregnancy or delivery, or in the infant, are shown for both groups in Table 3.

Delivery was performed by Caesarean section in 10 cases (8.1%, nine in low-dose group vs. one in high-dose group, N.S.). The reasons were severe inflammatory bowel disease in three, twin pregnancy in two, placental detachment in one case, and obstetrical difficulties or foetal distress in the other four cases.

Five cases of distress in the newborn were reported (four in the low-dose group and one in the high-dose group, N.S.). Three of these cases were premature babies. Details are shown in Table 3. None of these babies died.

Five infant abnormalities were reported (Table 3). They included one case of lethal oxalosis and four cases of malformations. The lethal oxalosis concerned a child

Table 2. Outcome of pregnancy in the subgroups of women who received 3 g/day or more of Pentasa mesalazine microgranules

Origin	Age	IBD	Mesalazine (g/day)			Outcome of pregnancy
			1st trim.	2nd trim.	3rd trim.	
F.R.			4	4	4	N (Normal)
F.R.	27	UC	4	4	4	N
F.R.	26	UC	4	4	4	N
G.U.	38	CD	3	4	4	N
F.R.	29	?	2	4	4	N
T.I.S.	23	UC	0	4	4	N
F.P.	27	CD	3	3	3	N
F.R.	?	?	3	3	3	N
F.R.	?	?	3	3	3	N
F.R.	?	?	3	3	3	N
F.R.	24	UC	3	3	3	Caesarean section
G.U.	23	CD	3	3	3	Prematurity, case no. 14
G.U.	?	CD	3	3	3	Fetal death, case no. 3
T.I.S.	23	UC	3	3	3	Prematurity, case no. 9
T.I.S.	26	CD	3	3	3	Prematurity, case no. 10
T.I.S.	28	UC	3	3	3	N
G.U.	24	CD	3	3	3	N
G.U.	25	CD	3	3	3	N
F.R.	28	UC	3	3	3	N
F.R.	30	UC	3	3	3	N
F.R.	27	?	3	3	3	N
T.I.S.	32	UC	3	3	3	N
G.U.	31	UC	3	3	3	N
T.I.S.	36	CD	3	3		Prematurity, case no. 11
F.P.	23	CD	3	2	2	N
F.R.	?	CD	3	2	2	N
F.P.	29	?	3	2	0	N
F.P.	?	?	3	0	0	N
F.R.	30	?	3	0	0	N
T.I.S.	26	CD	3	0	0	N
T.I.S.	25	CD	3	0	0	N
G.U.	29	CD	3	0	0	N
G.U.	36	CD	3	0	0	N
G.U.	?	CD	3	0	0	Abortion, case no. 2
F.R.	?	?	0	3	3	N
G.U.	25	CD	0	0	3	N
G.U.	32	CD	0	0	3	Prematurity and postnatal distress, case no. 13

F.P., Ferring prospective study; F.R., Ferring retrospective study; G.U., gastroenterology units; T.I.S., Teratogen Information Service.
case no., case number in Table 3.
IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease.

whose parents were first cousins. The mother was 38 years old, had ulcerative colitis, and had been given mesalazine (dose not mentioned) and loperamide during the first 2 months and the last month of pregnancy. Ultrasonographic examination of the foetus was normal at 24 weeks of pregnancy; delivery was uneventful. At 3 months, the infant developed severe anaemia and terminal renal insufficiency with nephrocalcinosis. Oxalosis was diagnosed on the basis of hyperoxalemia (243 μmol/L, normal <40), and hyperoxaluria (oxalate/creatinine ratio in urine 0.34, normal 0.03). The infant died of renal insufficiency a few days after diagnosis. The first case of malformation consisted of a congenital cataract. The mother had taken diosmectite, sulphasalazine (dose not specified) and 1 g/day of mesalazine throughout pregnancy; serological tests

ruled out rubella and toxoplasmosis. Pyloric stenosis was reported in twins whose mother had taken 3 g/day mesalazine and 500 mg/day ursodeoxycholic acid throughout pregnancy; the babies were treated surgically, and recovered fully. The last malformation was a congenital hip dislocation which was diagnosed at birth and resolved after medical treatment.

DISCUSSION

This study describes the outcome of 123 pregnancies (126 foetuses) in women given oral Pentasa mesalazine microgranules during pregnancy. Only one recent series to date had studied pregnancies in women receiving more than 3 g/day of mesalazine.[31] We confirm that low doses do not influence the fate of pregnancy, and show that doses of 3 g/day do not increase the risk of malformations.

Mesalazine is widely used to treat acute episodes of inflammatory bowel disease and for maintenance treatment. Small amounts of 5-ASA and acetyl-5-ASA are detectable in the maternal and cord plasma during treatment with sulphasalazine or mesalazine.[14, 15] Studies of large numbers of women have shown that sulphasalazine does not increase the risk of foetal complications.[4, 16] Earlier studies of series of women given 5-ASA during pregnancy included only few women who received low doses of mesalazine.[27–31] In the first of these studies,[27] which included 19 pregnancies, the mean daily dose of mesalazine was 1.7 g, and the highest dose was 2.4 g; a miscarriage was reported in a woman who had already miscarried four times before taking mesalazine. The second study[28] concerned 19 normal pregnancies in women given 1.2 g/day Asacol. For the third series, the outcome of pregnancy was reported for 11 women given mesalazine microgranules orally at a daily dose of 1.5–2.3 g.[29] The series comprised nine healthy babies, one spontaneous abortion (the woman had a uterine malformation), and one infant with malformations of the thumbs, single umbilical artery, and small placenta. In this case, however, the responsibility of mesalazine was ruled out, as the mother had not taken it during organogenesis.[29] No information on the fate of pregnancy was available in the literature for daily doses of mesalazine ≥3 g/day when Colombel *et al.* reported a case of severe foetal nephropathy,[30] in which the mother had taken 4 g/day of mesalazine during renal morphogenesis; the incrimination of mesalazine was envisaged because the renal lesions were unusual and reminiscent of those described in anuric neonates exposed *in utero* to indomethacin.[30, 32] Diav-Citrin *et al.* recently published a controlled cohort study which confirmed the safety of mesalazine at low doses in a series of 165 women with inflammatory bowel disease who were compared to matched controls.[31] They mentioned that 20.3% (i.e. 33) of the women received more than 3.2 g/day; however, the results of this subgroup were not analysed separately. In our series, 37 women ingested a daily dose of 3 g, and six a daily dose of 4 g.

We collected information from various sources, including the main gastroenterology units caring for inflammatory bowel disease patients in Paris, and the main pharmacovigilance unit specializing in pregnancy and drug-induced embryotoxicity (T.I.S.). Forty-five pregnancies were followed prospectively; the remaining 78 were assessed retrospectively. Only one adverse event was reported in the subjects followed prospectively, i.e. a case of intrauterine growth retardation. Because the study was not controlled, the question of the safety of mesalazine can only be addressed by analysing the potential causality of the drug in each reported adverse event.

Miscarriage is frequent in the general population, and is observed with increasing frequency in women with inflammatory bowel disease, especially when the disease is active (up to 35% of cases).[3–9, 12] In our series, there were only two cases of miscarriage (1.6%), which is probably due to the fact that many foetal losses are not recognized clinically.[9] We observed one case of foetal loss at 32 weeks of pregnancy. The natural risk of foetal loss after 16 weeks is around 1%, and our single case cannot therefore be considered as above this risk.[9] The risk of prematurity in inflammatory bowel disease women is clearly higher than in the general population, and varies between 7 and 25%.[3–8, 12] In the present series, the risk of premature delivery or intrauterine growth retardation was 9.5%. Interestingly, it was significantly higher (i.e. 13%) in the group of women who received large doses of mesalazine. Although the role of the drug cannot be ruled out, it is likely that the risk can be attributed to the inflammatory bowel disease. Such a risk has indeed already been mentioned in several studies of inflammatory bowel disease patients who received various treatments including mesalazine[31] and azathioprine.[18] Furthermore, in five of our 13 cases, mesalazine was not given during the last trimester. The cases of perinatal and postnatal distress

Table 3. Adverse events for women with inflammatory bowel disease given Pentasa mesalazine microgranules during pregnancy

Case no.		Age	IBD	Mesalazine (g/day) 1st trim.	2nd trim.	3rd trim.	Origin	Associated conditions
Abortions, foetal death, ectopic pregnancy								
1	abortion at 10 weeks		UC	1			T.I.S.	UC in remission, smoker, 8 g/day cholestyramine
2	abortion at 10 weeks		CD	3			G.U.	CD in remission, smoker, 8 g/day cholestyramine
3	foetal death at 32 weeks		UC	3	3	3	G.U.	UC in remission
4	ectopic pregnancy	37	UC	?			T.I.S.	Ectopic pregnancy
Prematurity, intrauterine growth retardation								
5	IUGR			2	0	0	F.P.	
6	prematurity (30 weeks)	37		2	2	2	F.R.	
7	prematurity (35 weeks)		CD	?	0	0	T.I.S.	Placental detachment, caesarean section
8	prematurity (29.5 weeks)	26	UC	1	0	0	T.I.S.	Acute appendicitis complicated by chorioamniotitis. Caesarean section. Apparent death of the infant necessitating reanimation.
9	prematurity (34 weeks)	26	UC	1	0	0	T.I.S.	Gemellary pregnancy. 500 mg/day ursodeoxycholic acid throughout pregnancy. Caesarean section. Pyloric stenosis in both infants.
10	prematurity (29 weeks)	26	CD	3	3	3	T.I.S.	Gemellary pregnancy. 5 mg/day prednisone throughout pregnancy.
11	IUGR	36	CD	3	3	0	T.I.S.	
12	postmaturity (5 days)	28	UC	0	0	2 + 1 enema	G.U.	No respiration at birth, artificial ventilation for 48 h.
13	prematurity	32	CD	0	0	3	G.U.	Prematurity due to small bowel perforation with peritonitis. Caesarean section. Respiratory distress, artificial ventilation for 5 days.
14	prematurity	23	CD	3	3	3	G.U.	15–40 mg/day prednisone throughout pregnancy. Prematurity due to flare up of Crohn's disease. Caesarean section.
15	prematurity	24	CD	1	0	0	G.U.	Familial mediterranean fever. Prematurity due to intoxication by food. Caesarean section.
Postnatal distress								
16	transient bradycardia from 6 h until 10 days of life	29	UC	1.5	0	0	T.I.S.	

8	Apparent death necessitating	26	UC	1	0	0	T.I.S.		Acute appendicitis complicated by reanimation chorioamniotitis. Caesarean section. Apparent death of the infant necessitating reanimation.
12	No respiration at birth	28	UC	0	0	2 + 1 enema	G.U.		
13	Respiratory distress	28	CD	0	0	3	G.U.		Prematurity due to small bowel perforation with peritonitis. Caesarean section. Respiratory distress, artificial ventilation for 5 days.
17	Infection at day 4 (*Streptococcus*)	37	CD	2	2	2	G.U.		
Diseases, Malformations									
18	Oxalosis, death at 3 months	38	UC	?	?	?	F.R.		
19	Cataract	23	UC	1	1	1	F.R.		
9	Pyloric stenosis in twins	23	UC	3	3	3	T.I.S.		Gemellary pregnancy. 500 mg/day ursodeoxycholic acid throughout pregnancy. Caesarean section. Pyloric stenosis in both infants
20	Bilateral hip dislocation	28	UC	1.5	1.5	1.5	T.I.S.		

F.P., Ferring prospective study; F.R., Ferring retrospective study; G.U., gastroenterology units; T.I.S., Teratogen Information Service.
IBD, irritable bowel disease; UC, ulcerative colitis; CD, Crohn's disease; IUGR, intrauterine growth retardation.

had the usual causes, including twin births, placental detachment, and severe inflammatory bowel disease. Here again, it was unlikely that mesalazine had any role in these complications. The case of lethal oxalosis was diagnosed as unrelated to mesalazine. Oxalosis is a congenital autosomal recessive metabolic disorder, and is caused by a deficiency of alanineglyoxylate aminotransferase.[33]

In the present series, four cases of malformation were reported out of 126 foetuses. The percentage of malformations (3.1%) is thus similar to that observed in the general population in France, i.e. 1.7–3.4%.[10, 11] Bortoli *et al.* recently reported five cases of malformations out of 95 foetuses born to women with inflammatory bowel disease (5.3%).[12] In our series, all of the mothers concerned except one had absorbed low doses of mesalazine. The case of congenital cataract was observed in a child whose mother had taken 1 g/day mesalazine together with sulphasalazine and diosmectite throughout pregnancy. The pyloric stenosis was observed in twins whose mother had taken 3 g/day of mesalazine throughout pregnancy. The bilateral hip dislocation was also observed in a baby whose mother had taken 1.5 g/day of mesalazine. Although mesalazine or the other drugs taken are unlikely to be involved in these malformations, the possibility cannot be ruled out. Note, however, that congenital cataract, pyloric stenosis and hip dislocation are among the most frequent spontaneous congenital abnormalities.[34, 35]

We conclude that at doses ≤2 g/day Pentasa is probably as safe as sulphasalazine during pregnancy. As regards subgroups of patients given ≥3 g/day, the results also seem reassuring. Because at the present time it not possible to establish whether or not high blood concentrations of 5-ASA constitute a risk for the foetal kidney, or the likelihood of such a risk, we agree with Colombel *et al.*[30] that information on high doses of mesalazine should be collected, that alternative treatments should be used preferentially, and that in case of treatment with high doses of mesalazine, the echogenicity of the foetal kidneys should be regularly monitored.

ACKNOWLEDGEMENTS

This study was supported by Laboratoire Ferring, Gentilly, France.

The authors thank the gastroenterologists, obstetricians and monitors of pharmacovigilance who provided the information analysed in this paper.

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