



Cyclosporine treatment of steroid-refractory ulcerative colitis during pregnancy



Journal:	<i>Inflammatory Bowel Disease</i>
Manuscript ID:	IBD-08-0232.R1
Wiley - Manuscript type:	Original Research Articles - Clinical
Date Submitted by the Author:	n/a
Complete List of Authors:	Branche, Julien; CHU Lille, Gastroenterology Cortot, Antoine; CHU Lille, Gastroenterology Bourreille, Arnaud; CHU Nantes, Institut des Maladies de l'Appareil Digestif Coffin, Benoit; Hopital Louis Mourier, Service d'Hépatogastroentérologie De Vos, Martine; Ghent University Hospital, Service d'Hépatogastroentérologie de Saussure, Philippe; Service d'Hépatogastroentérologie Seksik, Philippe; Hôpital Saint-Antoine, Service de Gastroentérologie et Nutrition Marteau, Philippe; Hôpital Lariboisière, Département médico-chirurgical de pathologie digestive Lemann, marc; Hôpital Saint Louis, Service de Gastroentérologie Colombel, Jean; CHU Lille, Gastroenterology
Keywords:	Immunomodulators < Clinical Areas, Pregnancy < Clinical Areas, Ulcerative Colitis: General Clinical < Clinical Areas



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Julien BRANCHE^{1,9} ; Antoine CORTOT^{1,9} ; Arnaud BOURREILLE^{2,9} ;
Benoît COFFIN^{3,9} ; Martine de VOS^{4,9} ; Philippe de SAUSSURE^{5,9} ; Philippe SEKSIK^{6,9} ;
Philippe MARTEAU^{7,9} ; Marc LEMANN^{8,9} ; Jean-Frédéric COLOMBEL^{1,9}

¹ Service des Maladies de l'Appareil Digestif et de la Nutrition, Hôpital Huriez, CHU Lille,
Lille, France

² Institut des Maladies de l'Appareil Digestif, CHU Hôtel-Dieu, Nantes, France

³ AP-HP, Hopital Louis Mourier, Service d'Hépatogastroentérologie, 92700 Colombes, France
and Université Paris VII, Paris, France

⁴ Service d'Hépto-Gastroentérologie, Ghent University Hospital , Belgique

⁵ Service d'Hépto-Gastroentérologie, Hôpital Cantonal Universitaire, Genève, Suisse

⁶ AP-HP, Service de Gastroentérologie et Nutrition, Hôpital Saint-Antoine, Paris, France

⁷ AP-HP, Département médico-chirurgical de pathologie digestive, Hôpital Lariboisière, Paris,
et université Paris 7, France

⁸ AP-HP, Service de Gastroentérologie, Hôpital Saint-Louis, Paris, France

⁹ GETAID, Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif,
Hôpital Saint Louis, Paris, France

Corresponding author :

Professor J-F Colombel, Department of Hepato-Gastroenterology, Hôpital Claude Huriez,
CHU Lille, 59037 Lille Cedex, France; Tel: (33) 3 20 44 47 14; Fax: (33) 3 20 44 47 13;

jfcolombel@chru-lille.fr

Abstract

Introduction: Cyclosporine is considered as a safe and effective treatment of severe steroid refractory ulcerative colitis. However, few data are available concerning its safety profile in pregnant women. We report here the experience of five GETAID centers.

Patients and methods: In a retrospective study data about patients with severe ulcerative colitis and treated with cyclosporine during pregnancy were extracted from medical records of consecutive patients treated between 2001 and 2007.

Results: Eight patients (median age 30.5-years-old) were identified. At the time of flare-up, median duration of pregnancy was 11.5 weeks of gestation (4-25). Seven patients had pancolitis. All patients had more than 3 commonly used clinical and biological severity criteria. Three patients had severe endoscopic lesions and 5 patients had not. All patients received IV corticosteroids for at least 7 days before introduction of cyclosporine. Two patients received azathioprine during treatment with cyclosporine. No severe infections or other complications due to treatment were observed. Treatment was effective in 7/8 patients. One patient received infliximab due to cyclosporine therapy failure with a good outcome. No colectomy was performed during pregnancy. Seven pregnancies were conducted to term, but one *in utero* death occurred due to maternal absence of S protein. Two newborns were premature, including one case of hypotrophy. No malformations were observed.

Conclusion: In our experience, treatment with cyclosporine for steroid-refractory ulcerative colitis during pregnancy can be considered as safe and effective.

Introduction

Inflammatory bowel diseases, and especially ulcerative colitis (UC), represent the major causes of severe acute colitis. A clinical response and/or remission can be obtained with intravenous steroid therapy in two-thirds of patients with severe acute colitis. Until the mid 1990s, colectomy was the only available option in case of refractoriness to steroid therapy [1-3]. Previous reports suggested that the risk of fetal death and maternal morbidity is increased in patients requiring surgery for severe acute colitis during pregnancy [4, 5]. Moreover, undergoing surgery for any indication while pregnant has been associated with a higher incidence of spontaneous abortion and preterm labor [6, 7]. Cyclosporine and, more recently, infliximab, offer new therapeutic strategies, and second-line medical treatment has become common.

Severe attacks of UC refractory to corticosteroids during pregnancy represents a clinical challenge. Disease activity during pregnancy is a worrisome obstetrical factor, with increased risk of fetal death [8]. Few data are available regarding cyclosporine treatment for severe steroid refractory UC during pregnancy. The literature is limited to isolated case reports [9-13]. Here we report our experience in this situation.

Patients and methods

A retrospective study was conducted by the GETAID (Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif). All the participants from the 35 centers of our group were asked to collect cases of patients with UC treated by cyclosporine during pregnancy between 2001 and 2007. The following data were extracted from medical files: date of birth, date of pregnancy, date of diagnosis of UC, date of onset of the severe flare-up, disease extent, Truelove and Witt's criteria [3], presence of severe endoscopic lesions defined by extensive deep ulcerations found on rectosigmoidoscopy [14], need for erythrocyte

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3 transfusion, duration of oral and intravenous steroid therapy, duration and dose of
4 cyclosporine therapy and concomitant medications. Outcomes include clinical response
5 assessed by the physician in charge of the patients, need for colectomy, complications and
6 drug toxicities. Date and mode of delivery, newborn status and occurrence of fetal
7 complications and malformations were also collected. Results are expressed as median, with
8 range shown in brackets. The general practitioners in charge of the patients and their children
9 and/or patients themselves were contacted by phone in august 2008 to have maximal follow-
10 up information regarding children health status.
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25 **Results**

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27 Eight pregnant women, median age 30.5 years (25–38) with severe attacks of UC
28 refractory to steroids and treated with cyclosporine during pregnancy were identified in five
29 GETAID centers. The median time interval to diagnosis was 34 months (8–144). At the time
30 of severe flare-up, the median duration of pregnancy was 11.5 weeks of gestation (4 – 25).
31 Seven patients (87.5 %) had pancolitis, and one had left colitis. All patients had more than 3
32 clinical and biological Truelove and Witt's criteria. Three patients had severe anemia with
33 need for erythrocyte transfusion. Three of eight patients had severe endoscopic lesions.
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43 All patients had received oral steroid therapy for a median duration of 14 days (1–148)
44 and then intravenous steroids for 7 days (6–7). All patients were initially given intravenous
45 cyclosporine therapy at a initial dose of 2 mg/kg/day (n=7) or 4 mg/kg/day (n=1) for a median
46 duration of 7 days (5–17). Seven of the 8 patients improved and cyclosporine was then orally
47 prescribed at a dose of 4 mg/kg/day twice a day. The remainder patient underwent 17 days of
48 intravenous cyclosporine but did not respond. This patient then received an infliximab
49 infusion and improved; perianal lesions occurred during the follow up and the diagnosis was
50 modified for Crohn's disease. Azathioprine was added in 2 patients at the time of oral
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3 prescription for cyclosporine. In responders, cyclosporine was continued for a median
4 duration of 107 days (7–253) and they were exposed to cyclosporine during pregnancy for a
5 median duration of 96 days (3–202). Cyclosporine levels were monitored in 6 out of 8
6 patients. Cyclosporine levels target were between 100 and 200 ng/ml and never exceeded 200
7 ng/ml. The remaining 2 patients received cyclosporine during 7 and 17 days respectively at a
8 dosage of 2mg/kg/day. Regarding steroid therapy, four patients were still on steroids at time
9 of delivery. In four patients steroids were stopped at time of delivery.

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20 No colectomy was necessary during pregnancy. After a median follow-up of 31
21 months (12–75), two colectomies were performed: one patient presented exacerbation of
22 symptoms immediately after delivery and required colectomy, and one patient had a relapse
23 requiring colectomy 3 years after delivery.

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No severe infection or any other complication due to cyclosporine was observed. One
patient had lip herpes recurrence during cyclosporine treatment and was treated locally with
success. One patient developed gestational diabetes treated with insulin during pregnancy.
Insulin therapy was stopped after discontinuation of steroid treatment.

Seven out of eight pregnancies were conducted to term. One *in utero* death occurred at
22 weeks of gestation in a patient who had received cyclosporine therapy for 90 days. This
death may be related to maternal S-protein deficiency. One year later, this patient
successfully carried a new pregnancy to term. Two newborns were premature (born at 33 and
32 weeks of gestation). One of them had a low birth weigh of 1,820 g while the other
premature newborn had a birth weigh of 3,340 g. The two mothers were receiving
cyclosporine since 3 and 14 days respectively and responded. Average newborn weight was
2,920 g (1,820 – 3,160). No birth defects were observed and all newborns were healthy.

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3 After a median follow up of 38 months (12 – 79) no renal side effect was clinically
4 detected in children. No blood test was performed in children. Regarding infectious outcome,
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6 no severe infection was observed in the first months of life of those children.
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15 **Discussion**

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17 In our series, cyclosporine appeared to be a well-tolerated and effective treatment and
18 for severe steroid refractory attacks of UC occurring during pregnancy. None of the eight
19 patients needed colectomy before delivery. No maternal or fetal serious side effects were
20 observed, with the exception of two premature delivery, occurring despite improvement of
21 colitis.
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29 Our series includes only a small number of patients but is the largest available in the
30 literature. Indeed, few data are available regarding the efficacy and tolerance of cyclosporine in
31 pregnant women with severe UC. Four papers reporting 5 cases have been published [9-12].
32 More recently Reddy *et al.* performed a case control study of pregnant patients with IBD
33 relapse among them 5 patients treated with cyclosporine [13]. Data regarding pregnancy and
34 birth outcome were only available in 3 patients. Characteristics of patients are summarized in
35 Table I and Table II.
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45 In our cohort, no maternal side effects due to cyclosporine therapy were observed. In
46 the literature, approximately half of the patients treated with cyclosporine had minor side
47 effects, such as paresthesia, hypertension, hypomagnesemia, hypertrichosis, headache, liver
48 abnormalities, gingival hypertrophy and hyperkalemia. As our series is retrospective, we
49 cannot exclude that such minor side-effects were missed. Major side effects, such as renal
50 failure, infection, convulsion or anaphylaxis [15] have been reported in up to 20% of UC
51 patients treated with cyclosporine. Dose reduction from 4 to 2 mg/kg/day reduces the
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3 frequency of these side-effects [16], and as only one patient received the 4 mg/kg/day initial
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5 dose in our series, this can explain the absence of toxicity observed in our patients.
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8 Cyclosporine is a pregnancy-category-C drug according to the FDA classification[17].
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10 This level of classification means that animal studies have shown significant toxicity, while
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12 no enough information on humans is available. So, category-C drugs can be cautiously given
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14 during pregnancy if a potential benefit outweighs the theoretical risk. Animal studies did not
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16 show increased malformation rate with cyclosporine but demonstrated risk for nephron
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18 reduction that led to systemic hypertension in rabbits [18-21]. In humans, cyclosporine has
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20 been extensively used after organ transplantation. In a meta-analysis including 15
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22 transplantation studies, 410 pregnancies were reported [22]. Cyclosporine did not appear to
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24 increase the malformation frequency. Also, no increase of the rate of prematurity or of low
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26 birth weight was found. Cyclosporine crosses the placental barrier and the newborn blood
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28 concentration is 10 to 50% of the blood concentration in exposed mothers, but the drug is
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30 rapidly eliminated after birth [23]. Two newborns were premature in our cohort but it is
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32 difficult to attribute these events to the use of cyclosporine because it has been demonstrated
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34 that IBD women have an increase risk of prematurity. A recent meta-analysis has indicated
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36 that the relative risk of prematurity is 1.8 and that the incidence of low birth weight is twice
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38 that of controls [24].
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45 Our results regarding efficacy of cyclosporine therapy for severe steroid refractory UC
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47 are similar to those found in the literature in non pregnant patients, where cyclosporine avoid
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49 early colectomy in 60 to 82% of cases [25-27]. Infliximab could constitute an alternative to
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51 cyclosporine in severe steroid refractory attacks of UC. This drug is effective for induction
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53 and maintenance therapy in moderate to severe UC refractory to conventional treatments
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55 (salicylates, steroids, azathioprine) [28]. However, in the Jarnerot *et al.* experience, infliximab
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57 appeared less effective in patients with "fulminant" UC (47% colectomy with infliximab vs
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3 69% with placebo at day 90) than in moderately severe patients (0% vs 62%) [29]. No data
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5 are available regarding the use of infliximab in severe attacks of UC during pregnancy. Safety
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7 data concerning the use of infliximab during pregnancy are reassuring. Infliximab is not
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9 teratogenic and does not impact on outcome of pregnancy [30, 31]. Infliximab is a pregnancy-
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11 category-B drug according to the FDA [17]. However, infliximab crosses the placental barrier
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13 and was detected in newborns from mothers treated with infliximab up to the sixth month of
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15 life [32, 33]. Low maternal concentrations of infliximab during childbirth have been
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17 associated with shorter exposure in newborns [32]. Consequences of the presence of
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19 infliximab in newborn blood during maturation of the immune system are still unknown. To
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21 date, the choice between infliximab and cyclosporine in severe steroid refractory UC poses a
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23 challenge. The two options are possible according to the recent ECCO consensus on UC [34].
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29 Thus, in our series of 8 cases, treatment with cyclosporine was effective over the short
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31 term and well-tolerated in severe steroid refractory attacks of UC during pregnancy. No
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33 maternal and fetal side effects were observed. These reassuring data are consistent with the
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35 previously reported cases.
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For Peer Review

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⁷ AP-HP, Département médico-chirurgical de pathologie digestive, Hôpital Lariboisière, Paris,
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⁸ AP-HP, Service de Gastroentérologie, Hôpital Saint-Louis, Paris, France

⁹ GETAID, Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif,
Hôpital Saint Louis, Paris, France

Corresponding author :

Professor J-F Colombel, Department of Hepato-Gastroenterology, Hôpital Claude Huriez,
CHU Lille, 59037 Lille Cedex, France; Tel: (33) 3 20 44 47 14; Fax: (33) 3 20 44 47 13;

jfcolombel@chru-lille.fr

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28 refractory to steroids and treated with cyclosporine during pregnancy were identified in five
29 GETAID centers. The median time interval to diagnosis was 34 months (8–144). At the time
30 of severe flare-up, the median duration of pregnancy was 11.5 weeks of gestation (4 – 25).
31 Seven patients (87.5 %) had pancolitis, and one had left colitis. All patients had more than 3
32 clinical and biological Truelove and Witt's criteria. Three patients had severe anemia with
33 need for erythrocyte transfusion. Three of eight patients had severe endoscopic lesions.
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43 All patients had received oral steroid therapy for a median duration of 14 days (1–148)
44 and then intravenous steroids for 7 days (6–7). All patients were initially given intravenous
45 cyclosporine therapy at a initial dose of 2 mg/kg/day (n=7) or 4 mg/kg/day (n=1) for a median
46 duration of 7 days (5–17). Seven of the 8 patients improved and cyclosporine was then orally
47 prescribed at a dose of 4 mg/kg/day twice a day. The remainder patient underwent 17 days of
48 intravenous cyclosporine but did not respond. This patient then received an infliximab
49 infusion and improved; perianal lesions occurred during the follow up and the diagnosis was
50 modified for Crohn's disease. Azathioprine was added in 2 patients at the time of oral
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3 prescription for cyclosporine. In responders, cyclosporine was continued for a median
4 duration of 107 days (7–253) and they were exposed to cyclosporine during pregnancy for a
5 median duration of 96 days (3–202). Cyclosporine levels were monitored in 6 out of 8
6 patients. Cyclosporine levels target were between 100 and 200 ng/ml and never exceeded 200
7 ng/ml. The remaining 2 patients received cyclosporine during 7 and 17 days respectively at a
8 dosage of 2mg/kg/day. Regarding steroid therapy, four patients were still on steroids at time
9 of delivery. In four patients steroids were stopped at time of delivery.
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20 No colectomy was necessary during pregnancy. After a median follow-up of 31
21 months (12–75), two colectomies were performed: one patient presented exacerbation of
22 symptoms immediately after delivery and required colectomy, and one patient had a relapse
23 requiring colectomy 3 years after delivery.
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30 No severe infection or any other complication due to cyclosporine was observed. One
31 patient had lip herpes recurrence during cyclosporine treatment and was treated locally with
32 success. One patient developed gestational diabetes treated with insulin during pregnancy.
33 Insulin therapy was stopped after discontinuation of steroid treatment.
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39 Seven out of eight pregnancies were conducted to term. One *in utero* death occurred at
40 22 weeks of gestation in a patient who had received cyclosporine therapy for 90 days. This
41 death may be related to maternal S-protein deficiency. One year later, this patient
42 successfully carried a new pregnancy to term. Two newborns were premature (born at 33 and
43 32 weeks of gestation). One of them had a low birth weigh of 1,820 g while the other
44 premature newborn had a birth weigh of 3,340 g. The two mothers were receiving
45 cyclosporine since 3 and 14 days respectively and responded. Average newborn weight was
46 2,920 g (1,820 – 3,160). No birth defects were observed and all newborns were healthy.
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3 After a median follow up of 38 months (12 – 79) no renal side effect was clinically
4 detected in children. No blood test was performed in children. Regarding infectious outcome,
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6 no severe infection was observed in the first months of life of those children.
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10 11 12 13 14 15 **Discussion**

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17 In our series, cyclosporine appeared to be a well-tolerated and effective treatment and
18 for severe steroid refractory attacks of UC occurring during pregnancy. None of the eight
19 patients needed colectomy before delivery. No maternal or fetal serious side effects were
20 observed, with the exception of two premature delivery, occurring despite improvement of
21 colitis.
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29 Our series includes only a small number of patients but is the largest available in the
30 literature. Indeed, few data are available regarding the efficacy and tolerance of cyclosporine in
31 pregnant women with severe UC. Four papers reporting 5 cases have been published [9-12].
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33 More recently Reddy *et al.* performed a case control study of pregnant patients with IBD
34 relapse among them 5 patients treated with cyclosporine [13]. Data regarding pregnancy and
35 birth outcome were only available in 3 patients. Characteristics of patients are summarized in
36 Table I and Table II.
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45 In our cohort, no maternal side effects due to cyclosporine therapy were observed. In
46 the literature, approximately half of the patients treated with cyclosporine had minor side
47 effects, such as paresthesia, hypertension, hypomagnesemia, hypertrichosis, headache, liver
48 abnormalities, gingival hypertrophy and hyperkalemia. As our series is retrospective, we
49 cannot exclude that such minor side-effects were missed. Major side effects, such as renal
50 failure, infection, convulsion or anaphylaxia [15] have been reported in up to 20% of UC
51 patients treated with cyclosporine. Dose reduction from 4 to 2 mg/kg/day reduces the
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3 frequency of these side-effects [16], and as only one patient received the 4 mg/kg/day initial
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5 dose in our series, this can explain the absence of toxicity observed in our patients.
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8 Cyclosporine is a pregnancy-category-C drug according to the FDA classification[17].
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10 This level of classification means that animal studies have shown significant toxicity, while
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12 no enough information on humans is available. So, category-C drugs can be cautiously given
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14 during pregnancy if a potential benefit outweighs the theoretical risk. Animal studies did not
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16 show increased malformation rate with cyclosporine but demonstrated risk for nephron
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18 reduction that led to systemic hypertension in rabbits [18-21]. In humans, cyclosporine has
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20 been extensively used after organ transplantation. In a meta-analysis including 15
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22 transplantation studies, 410 pregnancies were reported [22]. Cyclosporine did not appear to
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24 increase the malformation frequency. Also, no increase of the rate of prematurity or of low
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26 birth weight was found. Cyclosporine crosses the placental barrier and the newborn blood
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28 concentration is 10 to 50% of the blood concentration in exposed mothers, but the drug is
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30 rapidly eliminated after birth [23]. Two newborns were premature in our cohort but it is
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32 difficult to attribute these events to the use of cyclosporine because it has been demonstrated
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34 that IBD women have an increase risk of prematurity. A recent meta-analysis has indicated
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36 that the relative risk of prematurity is 1.8 and that the incidence of low birth weight is twice
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38 that of controls [24].
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45 Our results regarding efficacy of cyclosporine therapy for severe steroid refractory UC
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47 are similar to those found in the literature in non pregnant patients, where cyclosporine avoid
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49 early colectomy in 60 to 82% of cases [25-27]. Infliximab could constitute an alternative to
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51 cyclosporine in severe steroid refractory attacks of UC. This drug is effective for induction
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53 and maintenance therapy in moderate to severe UC refractory to conventional treatments
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55 (salicylates, steroids, azathioprine) [28]. However, in the Jarnerot *et al.* experience, infliximab
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57 appeared less effective in patients with "fulminant" UC (47% colectomy with infliximab vs
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3 69% with placebo at day 90) than in moderately severe patients (0% vs 62%) [29]. No data
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5 are available regarding the use of infliximab in severe attacks of UC during pregnancy. Safety
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7 data concerning the use of infliximab during pregnancy are reassuring. Infliximab is not
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9 teratogenic and does not impact on outcome of pregnancy [30, 31]. Infliximab is a pregnancy-
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11 category-B drug according to the FDA [17]. However, infliximab crosses the placental barrier
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13 and was detected in newborns from mothers treated with infliximab up to the sixth month of
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15 life [32, 33]. Low maternal concentrations of infliximab during childbirth have been
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17 associated with shorter exposure in newborns [32]. Consequences of the presence of
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19 infliximab in newborn blood during maturation of the immune system are still unknown. To
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21 date, the choice between infliximab and cyclosporine in severe steroid refractory UC poses a
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23 challenge. The two options are possible according to the recent ECCO consensus on UC [34].
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29 Thus, in our series of 8 cases, treatment with cyclosporine was effective over the short
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31 term and well-tolerated in severe steroid refractory attacks of UC during pregnancy. No
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33 maternal and fetal side effects were observed. These reassuring data are consistent with the
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35 previously reported cases.
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For Peer Review

	Age	Term of pregnancy	IV steroids (days)	IV cyclosporine (days)	Oral cyclosporine (days)	Clinical response	Term of delivery (WG)	Birth weight	Malformative syndrome	Mother's side effects	Colectomy
Bertschinger <i>et al.</i> [8]	23	27	N/A	10	77	Yes	34 – Caesarean section	2070g	No	Hypertrichosis	No
Jayaprakash <i>et al.</i> [5]	36	12	17	15	Yes	Yes	32 – Caesarean section	2070g	No	Transient mild renal impairment	No
Angelberger <i>et al.</i> [6]	21	15	9	21	Yes	Yes	29 - Caesarean section	893g	No	Hypertrichosis	Yes post delivery
Reindl <i>et al.</i> [7]	31	N/A	Yes	7	Yes	Yes	36 – Vaginal delivery	N/A	No	Hirsutism	No
	34	15	7	21	Yes	Yes	25 - Caesarean section	N/A	No	Hypertrichose	No
Reddy <i>et al.</i> [9]	29	24	14	8	N/A	Yes	26	1080g	N/A	N/A	N/A
	25	25	12	5	N/A	Yes	39	1968g	N/A	N/A	N/A
	30	15	4	3	N/A	Yes	Abortion at week 15	-	-	N/A	No
	27	14	13	9	N/A	Yes	N/A	N/A	N/A	N/A	N/A
	29	8	11	8	N/A	Yes	N/A	N/A	N/A	N/A	N/A

Table I: Characteristics of patients treated with cyclosporine during pregnancy, summary of the literature review:

WG: weeks of gestation; N/A: information not available

	Age	Term of pregnancy	IV steroids (days)	IV cyclosporine (days)	Oral cyclosporine (days)	Clinical response	Term of delivery (WG)	Birth weight	Malformative syndrome	Mother's side effects	Colectomy
Patient 1	38	27	7	7	30	Yes	32 – Vaginal delivery	1820g	No	No	Yes post delivery
Patient 2	32	6	7	5	192	Yes	37	2600g	No	No	Yes post delivery
Patient 3	29	15	7	5	98	Yes	36	3000g	No	No	No
Patient 4	28	14	7	7	0	Yes	33 – Vaginal delivery	3340g	No	No	No
Patient 5	30	10	7	7	104	Yes	Fetal death at week 22	-	No	No	No
Patient 6	25	13	6	17	0	No	35 - Caesarean section	3160g	No	No	No – Crohn's disease
Patient 7	31	24	7	9	244	Yes	37 – Vaginal delivery	2710g	No	No	No
Patient 8	32	10	7	0	200	Yes	37 – Vaginal delivery	2920g	No	No	No

Table II: Characteristics of patients treated with cyclosporine during pregnancy, our experience (patients 1 to 8) :

WG: weeks of gestation; N/A: information not available