Budesonide Induction and Maintenance Therapy for Crohn's Disease During Pregnancy

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Background: There is no standard approach for the medical management of Crohn's disease (CD) during pregnancy and there is limited data regarding safety and efficacy of the treatments. Budesonide (Entocort® EC, AstraZeneca) is an enteric coated locally acting glucocorticoid preparation whose pH- and time-dependent coating enables its release into the ileum and ascending colon for the treatment of mild to moderate Crohn's disease. There is no available data on the safety of using oral budesonide in pregnant patients.

Methods: We reviewed our Inflammatory Bowel Disease (IBD) center database to identify patients with CD who received treatment with budesonide for induction and/or maintenance of remission during pregnancy and describe the maternal and fetal outcomes in a series of eight mothers and their babies.

Results: The mean age of the patients was 27.7 years. All patients had small bowel involvement with their CD. The disease pattern was stricturing in 6 patients, fistulizing in 1 and inflammatory in 1 patient. Budesonide was used at the 6 mg/day dose in 6 patients and 9 mg/day dose in 2 patients. The average treatment duration ranges from 1-8 months. There were no cases of maternal adrenal suppression, glucose intolerance, ocular side effects, hypertension or fetal congenital abnormalities.

Conclusion: Budesonide may be a safe option for treatment of CD during pregnancy.

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Key Words: budesonide, Crohn's disease, pregnancy, partial small bowel obstruction, IBD

Crohn's disease (CD) commonly affects young adults in their reproductive years with ≈25% of women conceiving after a diagnosis of CD.[1] Most studies have shown fertility rates in CD to be equivalent to that of the general population.[2,3] Several studies have documented higher rates of adverse pregnancy outcomes in patients with inflammatory bowel disease (IBD). While some authors proposed that disease activity during conception or pregnancy may be associated with higher rates of adverse outcomes,[2,4,5] other studies have failed to find such an association.[6] Many of the large registry-based studies examining pregnancy outcomes have also been limited by the inability to accurately ascertain disease activity.[7–10] The frequency of relapse in patients who conceive while in remission is similar to that of the nonpregnant CD patient, but two-thirds of the patients who conceive at the time of active disease will have persistent or worsening disease activity during the course of their pregnancy.[1] Controlling disease activity prior to and during pregnancy is, thus, important in order to achieve optimal maternal and fetal outcomes.

There is no standard approach to the use of therapeutic agents for the management of CD during pregnancy, with limited data regarding safety and efficacy. Systemic (oral and parenteral) corticosteroids are sometimes necessary for the induction and maintenance of remission in CD patients. Their use during pregnancy has been associated by some authors with the theoretical risk of fetal adrenal suppression and congenital anomalies including cleft lip, while other studies identified no adverse effects.[2,11–13] Prolonged use of steroids has also been associated with significant maternal side effects including glucose intolerance, hypertension, and ocular side effects.

Budesonide (Entocort EC, AstraZeneca, Wilmington, DE) is an enteric coated locally acting glucocorticoid preparation whose pH- and time-dependent coating enables its release into the ileum and ascending colon for the treatment of mild to moderate CD.[14] After oral administration it undergoes extensive first-pass metabolism in the liver with a low systemic bioavailability (9%–21%).[14] It has been demonstrated to have a superior safety profile compared to systemic corticosteroids[15] but there are no available data on the safety of oral budesonide use for CD during pregnancy.

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We reviewed our IBD center database to identify patients with CD who underwent treatment with budesonide during pregnancy. We describe the maternal and fetal outcomes of a series of 8 such patients.

MATERIALS AND METHODS

This was a retrospective study from a single academic tertiary referral hospital. We reviewed our IBD center database to identify patients who had received budesonide for treatment of CD during pregnancy. Our database has been described in previous publications from our center[16] and includes information on age, race, duration of disease, and age at diagnosis. Disease extent (small bowel, large bowel, or both) and behavior (inflammatory, structuring, fistulizing) were classified using the Montreal classification.[17] We reviewed all inpatient and outpatient medical records and abstracted information about the history of treatment for their CD and noted both present and past use of steroids, immunomodulators (azathioprine/6-mercaptopurine, methotrexate), and biologics (infliximab, adalimumab) use, and the need for surgery to treat complications of CD.

All these patients were followed in combination by their obstetricians and our IBD center throughout the course of their pregnancy. We recorded information regarding the fetal outcomes including period of gestation, mode of delivery, birth weight, and the presence of congenital anomalies. We also examined the occurrence of any maternal adverse effects. All information was maintained in a Microsoft Excel (Redmond, WA) database and was analyzed using descriptive statistics.

This study was approved by the Institutional Review Board of the Medical College of Wisconsin.

RESULTS

There were a total of 539 female patients with CD who underwent treatment at our center during the study period 2001–2006. There were 60 pregnancies in 41 women. Of these 41 women, 8 patients received treatment with budesonide during their pregnancy and were included in our study.

Patient Characteristics

Table 1 describes the demographic information, CD characteristics, treatment history, and pregnancy outcomes in the study patients. The mean age of the patients was 27.7 years (range 21–32 years). All patients had small bowel involvement with their CD, while 3 patients had concomitant colonic involvement. The disease pattern was stricturing in 6 of the patients, while 1 patient had associated fistulizing disease and 1 patient had purely lumenal inflammatory disease. Half the patients had required surgery at some point related to the complications of their CD (2 patients with terminal ileal resection [TIR], 2 patients with ileocolectomy).

Disease Treatment During Pregnancy

All 8 patients received budesonide for induction of remission, and of these, 5 women received long-term maintenance therapy throughout their pregnancy (Table 1). Symptoms consistent with partial small bowel obstruction or CD flare prompted initiation of treatment in all 8 patients. The treatment duration ranged from 1–8 months. Six patients were maintained on a 6 mg daily dose of budesonide while 2 patients required 9 mg/day. Seven patients had budesonide initiation during the first trimester, while 1 patient was started on it only during the third trimester. Seven patients were maintained on budesonide up to the delivery. Four of the patients were on other agents for maintenance therapy at the time of initiation of budesonide. Among these, 1 patient was on concomitant sulfasalazine therapy. Three of the patients experienced a flare while on maintenance azathioprine therapy and budesonide was introduced to their regimen to induce and maintain remission.

Five patients experienced no further disease activity during their pregnancy while on maintenance budesonide. One patient (Patient 1) had symptomatic abdominal adhesions related to prior bowel surgery and was maintained on budesonide for 1 month in her first trimester prior to surgical intervention and lysis of adhesions. Following surgery, budesonide was discontinued and she was maintained on azathioprine until her delivery at term of a healthy infant. Another patient with ileocolonic CD (Patient 3) who was on methotrexate prior to conception was maintained on budesonide from her first trimester without any disease activity until 35 weeks of gestation, when she developed abdominal pain and diarrhea. She underwent emergent cesarean section for fetal heart decelerations and delivered a healthy baby. One of the patients (Patient 2) developed partial small bowel obstruction at 6 weeks requiring hospitalization and intravenous steroids. She was then started on budesonide, which was continued throughout her pregnancy. An attempt to taper off the budesonide at 26 weeks resulted in the recurrence of symptoms and she was continued on 6 mg/day of budesonide until a spontaneous vaginal delivery of a healthy infant at term with no further disease exacerbations.

Pregnancy and Safety Outcomes

Seven patients carried their pregnancy to full term (>38 weeks), while 1 patient delivered at 35 weeks. There were no cases of spontaneous abortions. One patient underwent emergent cesarean section while the other 7 patients had normal spontaneous vaginal deliveries. There were also no congenital anomalies noted in the babies. To date, there are no fetal adverse effects secondary to budesonide noted in any of the patients. We also did not identify any fetal or maternal adverse effects related to budesonide including adrenal suppression, ocular side effects, hyperglycemia, gestational dia-

TABLE 1. Disease Characteristics and Pregnancy Outcomes of 8 CD Patients Treated with Budesonide During Pregnancy

Patient No.	Disease Location/ Surgical History	Pregnancy Age	Time of Treatment Initiation	Treatment Duration	Budesonide Dose	Concomitant Medications	Outcomes
1	SB-I,S Ileocolectomy with anastomosis	21	1st trimester	1 month	6 mg daily	Azathioprine B12, FA, MVI	Healthy, full term
2	SB/LB-I	31	1st trimester	1st, 2nd, 3rd trimester (6 months)	6 mg daily-failed taper at 26 weeks	B12, FA, MVI	Healthy, full term
3	SB/LB Ileocecal resection with right hemicolectomy	32	1st trimester	1st, 2nd, 3rd trimester (8 months)	6 mg daily	MTX-discontinued prior to conception MVI	Emergent c-section at 35 weeks due to fetal distress, healthy infant
4	SB/LB-I,S	30	1st trimester	1st, 2nd, 3rd trimester	6 mg daily	Azathioprine Miralax, MVI	Healthy, full term
5	SB-S TIR	26	1st trimester	1st, 2nd, 3rd trimester	9 mg daily	Azathioprine MVI	Healthy, full term
6	SB-S TIR	32	3rd trimester	12 weeks	6 mg daily	Miralax, FA, MVI, MTX discontinued prior to conception	Healthy, full term
7	SB-S,F	25	1st trimester	1st, 2nd, 3rd trimester	6 mg daily	TPN- 1st trimester Lovenox	Healthy, full term
8	SB-I,S	25	1st trimester	1st, 2nd, 3rd trimester	9 mg daily	Sulfasalazine, B12, cholestyramine	Healthy, full term

SB, small bowel; LB, large bowel; I, inflammation; S, strictures; F, fistulizing; TIR, terminal ileum resection; FA, folic acid; MVI, multivitamin; MTX, methotrexate; full term, ≥38 weeks.

betes, hypertension, preeclampsia, or infectious complications.

DISCUSSION

CD often affects women in their reproductive years. Control of disease activity prior to conception and during pregnancy is important. To our knowledge, the use of budesonide for CD during pregnancy has not been reported previously. We present 8 patients with CD who were treated with budesonide during pregnancy and achieved good maternal disease control and fetal outcomes with no clear steroid-related adverse effects.

In our patients, budesonide as a single agent for the treatment of CD was sufficient to induce remission in 4 women, while it was added to the maintenance regimen of 4 patients who experienced flare activity. Randomized controlled trials have shown budesonide to be efficacious in the induction of remission and maintenance up to 6 months.[18–25]

The primary concern related to use of conventional steroids in CD, irrespective of pregnancy status, is the high frequency of steroid-related adverse effects, including opportunistic infections, adrenal suppression, hyperglycemia, hypertension, and ocular and bone changes. Budesonide offers the advantage of a lower incidence of these side effects.[15] In our series we did not identify any adverse maternal or fetal outcomes related to budesonide use. Budesonide is considered an FDA class C drug for use in pregnancy, which means that while animal studies may have shown an adverse effect on the fetus, there are no adequate studies in humans. There are limited data on the safety of budesonide during treatment of CD in pregnancy; however, previous studies have examined the safety of inhaled budesonide for treatment of asthma in pregnant patients. Two large registry-based studies from Sweden of ≈2000 female patients each using inhaled budesonide for management of asthma did not identify an increased rate of prematurity, low birth weight, or congenital malformations.[26,27] Other smaller studies have documented similar results.[28] Studies in CD comparing budesonide to the use of prednisone both in children[29] and adults[30–33] have noted fewer side effects in the budesonide group. Similar rates of

adverse effects in the 2 groups were also noted in the placebo-controlled studies of budesonide.[18,21] Our study adds to the data supporting the low rate of systemic side effects seen previously, and thus supports the consideration of budesonide use during CD pregnancy.

Our study has a few limitations. The small sample size and the single-institution tertiary referral center design warrant caution while generalizing our results to all pregnant patients with CD.

In conclusion, ours is the first report of the use of budesonide to induce and maintain remission of CD during pregnancy. In our series of women receiving budesonide during pregnancy, there was no clear evidence of adverse effects and we were able to successfully control disease activity, resulting in good clinical outcomes for mother and baby. There is a need for a large multicenter studies examining safety and efficacy of the use of budesonide in CD during pregnancy.

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