

## CROHN'S DISEASE DURING PREGNANCY

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### ABSTRACT

**Introduction:** Inflammatory bowel disease (IBD) often affects women during their childbearing years. Indications for surgery, in pregnant patients, are the same as for non-pregnant women and include perforation, obstruction, haemorrhage, fistula and abscess. The controlling of the activity of the disease is the main determinant of the good prognosis of pregnancy.

**Case report:** a woman with abdominal pains required surgical treatment during pregnancy. She underwent two consecutive laparotomies. Histological diagnosis was: Crohn Disease (CD). After surgery the patient was treated with antibiotic and anti-fungal therapy because of a *Candida albicans* infection. After 5 months it was performed an ileostomy closure with bowel recanalization. The later postoperative course was free of complications and, after surgical care, infliximab was introduced again.

**Discussion:** CD doesn't seem to have effects on fertility when it is inactive, whereas if it's active seems to reduce fertility. The treatment with target therapy (infliximab), had a positive outcome. Generally, medical treatment for active disease in pregnant patients is the same as for non-pregnant women, except for antiproliferative drugs as methotrexate. CD occurring during pregnancy is a pathology that needs a multidisciplinary approach, but thanks to the new drugs it's possible a good control of the pathology during the gestation.

**Key words:** Inflammatory bowel disease, Crohn's disease, Pregnancy, Surgery, Target therapy.

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### Introduction

Crohn's Disease (CD) is an inflammatory bowel disease (IBD) that commonly affects people in the second or the third decade of life.

Therefore, frequently it affects women during their reproductive years and in childbearing age. When it occurs, the disease may be detrimental to the outcome of pregnancy or the pregnancy may adversely affect the course of the disease<sup>(1-3)</sup>.

About 25% of women affected by inflammatory bowel disease conceive. In literature, about one-third of patients in remission CD will present a relapse in the following pregnancy (no difference with non-pregnant women) and if conception occurs at a time of active disease two thirds have persistent activity and of these, two thirds will deteriorate<sup>(4)</sup>.

Actually little evidence exists to help clinical decision making for the treatment of CD in pregnant patients. Indications for surgery in pregnant patients are the same as for non-pregnant women and

include perforation, obstruction, haemorrhage, fistula and abscess<sup>(5)</sup>. CD seems to affect fertility, reducing the chance of pregnancy through different mechanisms as tube and ovarian inflammation, perianal disease and previous CD surgical interventions.

Prognosis of the underlying disease during pregnancy is believed to depend strongly on the inflammatory activity at the time of conception, although there are conflicting opinions in literature on this topic. A 2007 meta-analysis<sup>(6)</sup> in pregnant women with IBD shows in CD patients an increase in the incidence of preterm delivery, low birth weight, and caesarean section but no increase in the risk of congenital abnormalities, of small for gestational age (SGA) and of stillbirths.

Hatch et al studied the impact of pregnancy on surgical Crohn disease and they found much higher rates of ano-rectal suppuration and intestinal-genitourinary fistulas and substantially lower rates of bowel obstruction and/or stricture in pregnant; however pregnancy was associated with higher

rates of overall surgical disease<sup>(7)</sup>. If surgery is required, abortion-stillbirth rates are reported to be considerably increased<sup>(8)</sup>. We present a case report of CD in 31 years old woman requiring surgical interventions during pregnancy.

### Case report

The patient V.A. came to our centre on Sept. 2010 at the age of twenty-eight. At the medical history presented thalassaemic trait and reported an appendectomy at the age of sixteen. No evidence of IBD or gastro-intestinal tumours on her family history. She was a smoker (5-6 cigarettes/die), an occasional alcohol drinker, and usually she had two coffees/die.

For several years patient referred a postprandial diarrhoea and in the early months of 2010 she had a worsening of the symptoms with about eight bloodless evacuations a day, severe abdominal pain and fever.

On April of 2010, for the appearance of continuous vomiting, she was hospitalized in a surgical department. The blood tests showed an increase of inflammatory indicators, anaemia and high platelets count. Colonoscopy points out a sub-stenotic ileocecal valve, with an eroded and congested mucosa, and some ulcerations covered by fibrin at the last ileal loop, without evidences of any disease in the colon. That was compatible with an active Crohn's disease. Therefore the patient was treated with steroids i.v. (intravenous) and, after a clinical benefit, she was discharged with a therapy based on beclometasone, mesalamine and rifaximin. During the follow up she had some recurrences (Tab. 1).

Recurrence (after Diagnosis)	Symptoms	Treatment
4 months	Abdominal pain vomiting and constipation	Mesalamine, PPI and prednison
14 months	Abdominal pain and vomiting	Mesalamine, PPI and prednison
17 months	Sub-occlusive episode	Start Infliximab
24 months	Abdominal pain vomiting and weight loss	Infliximab

**Table 1:** Clinical Course.

On the last days of April the patient discovered to be pregnant. Physician started to treat the patient with infliximab with a gradual reduction of steroids assay. We executed four assays of infliximab till the III trimester of pregnancy.

In November 2012 (35<sup>th</sup> gestation week) the patient referred abdominal pain, mainly in the right iliac fossa and on the right flank associated with fever. MR (Magnetic resonance) detected sub-phrenic air sickle, with the last ileal loops thickened

and stiff. Therefore surgery, with a caesarean delivery and an exploratory laparotomy, was performed.

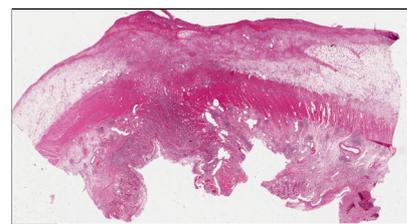
After the caesarean delivery, the intestinal loops were analysed and it was found a large abdominal spillage, mainly in Douglas cavum. The last iliac loop appeared strongly bloated, covered by fibrin with a lively inflammatory process; it was found a unique perforation quickly treated with a raffia, a protective ileostomy and a peritoneal washing. Patient gave birth to a 1670g-weight infant, without any malformation. The patient's high was 158 cm and her weight after delivery was 45 Kg (18.97 BMI).

After surgery the antibiotic Ceftriaxone 2 gr i.v./die and the broad spectrum antibiotics Imipenem 500 mg x 3/die i.v. were administrated. After 36 hours without fever or complications, reappeared signs of peritonitis and a fever of 38.5 °C, despite antibiotic treatment. It was decided a second laparotomy: there was no discontinuity in raffia but it was decided to resect the distal ileal loops that were compromised because of the inflammatory process (Table 2).

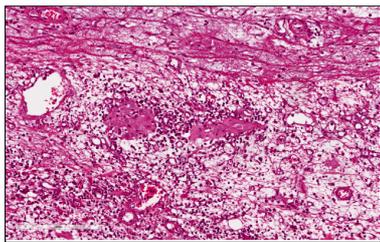
	WBC (x103/mm3)	TEMPERATURE	CRP (mg/dl)	ESR (mm/h)
At 1 <sup>st</sup> surgery	9.86	37.8	12	89
At 2 <sup>nd</sup> surgery	12.00	39.00	31	71
2 day after	12.64	38.5	33	47
4 days after	14.83	37.9	37	38
15 day after	8.80	36.5	5.15	13
	White Blood Cells	(°C)	C Reactive Protein	Erythrocyte Sedimentation Rate

**Table 2:** Lab test results and temperature.

The histological report diagnosed with Crohn's disease, stenosis and obstruction in the terminal ileum with fistulas and the visceral peritoneum with multiple abscesses formation. There were presence of aphthoid ulcers in the mucosa and chronic mild inflammation in the submucosa (Fig. 1-2).



**Figure 1:** (5x) erosion of the mucosa (SKIP LESION), transmurial pattern of inflammation penetrating the wall and peritonitis (acute phlogosis and fibrous exudate coating).



**Figure 2:** (40X) epithelioid granulomas, characteristic histological feature of Crohn's disease.

The antibiotic therapy was Imipenem 500 mg x 3/die i.v. and Metronidazole 500 mg x 3/die i.v. After 2 days the Imipenem was replaced with Meropenem 500 mg x 3/die i.v. As the fever didn't fall, a fungal and a bacteriological testing were carried in abdominal drainage, with positivity for the *Candida Albicans*; for this reason it was added the Fluconazole 200 mg x 2/die i.v.

Two days after, on the advice of the specialists in infectious diseases, metronidazole was replaced with Ciprofloxacin 200 mg x 2/die i.v. The later postoperative course was free of complications and after surgical care the infliximab was restarted. After 5 months it was performed an ileostomy closure with bowel recanalization.

## Discussion

At the time of conception the disease activity seems to influence the course of the disease. If conception occurs during a period of remission, the incidence of relapses during pregnancy is similar to controls. A retrospective study, including 70 pregnancies in 61 patients with Crohn's disease, observed a small but significant decrease in the Harvey-Bradshaw index of disease activity during pregnancy, in comparison with the year preceding and following the pregnancy.

In this study, the clinical improvement of the disease in pregnancy was partly due to the reduction of tobacco smoke during that period<sup>(9)</sup>. If, however, conception occurs at the time of active disease, most of patients have persistent activity with further risks during pregnancy<sup>(10-11)</sup>. The intervals between surgical procedures are longer in patients with a previous pregnancy; in fact those require fewer resections, when compared with nulliparous women with Crohn's disease.

Therefore, women with Crohn's disease have a lower relapse rate in the year after pregnancy than in the year before pregnancy, probably by an immunomodulating effect of gestation. Patients with active perianal or rectal disease should be

advised to have a caesarean section.

Although many authors prefer caesarean section in all the pregnancies affected by CD, vaginal delivery should be the standard practice especially for women with quiescent disease or mild inflammation, because the differences were not statistically significant in literature<sup>(12)</sup>. Ileo-anastomosis with ileal pouch in a pregnant patient with Crohn's disease is still a rarity, but it's an indication for caesarean section<sup>(13)</sup>. Patients with colostomy or ileostomy can deliver vaginally, but if there is an elevated obstetric risk, a caesarean section could be considered. In this case report the patient showed a reactivation of the disease and the caesarean delivery before the end of gestation seemed the only possible decision to save both mother and son.

Indications for surgery in pregnant patients are the same as for no-pregnant women and include perforation, obstruction, haemorrhage, and abscess. In particular, a MR showed subphrenic air sickle, with the last ileal loops thickened and stiff. In patients with severe CD, untreated disease is a much higher risk for the fetus than surgical treatment: it include proctocolectomy, hemicolectomy, segmental resection and ileostomy.

A temporary ileostomy is generally preferred in order to reduce postoperative complications after primary anastomosis<sup>(14)</sup>; for this reason it was decided to resect the distal ileal loops and to programme a following ileostomy closure with bowel recanalization. In women with CD in pregnancy, as the main risk depends more by the activity of the disease, it is preferable to continue a maintenance drug therapy to avoid a possible relapse.

Generally, medical treatment for active disease in pregnant patients is the same (Table 3) as for no-pregnant women, except methotrexate, because the risks exceed any benefit. Folic Acid, vitamin B12, vitamin B6, probiotics and iron supplementation are recommended for all pregnant women<sup>(15-18)</sup>.

Biological therapy during conception and pregnancy causes great concern to physician and patient. Till now there is no evidence about associations between anti-TNF $\alpha$  (Tumor necrosis factor) and embryotoxicity, teratogenicity or abortions, however, they must be used carefully in pregnancy, because their safety in gestation is not clear.

Women in childbearing age, in treatment with anti-TNF $\alpha$ , must avoid conception. If this treatment is necessary in pregnancy in order to control the activity disease, benefits overcome risks, mainly in first and second trimester. The patients continue the

therapy with infliximab till the III trimester of pregnancy. The two largest studies about infliximab (IFX) safety in pregnancy come from TREAT registry. No evidence of congenital abnormalities in any patient was found. There are no evidences about use of IFX during breastfeeding period, except some case reports that suggest placental transfer in breastfeeding. Actually it seems to be safe IFX use during breastfeeding<sup>(19)</sup>.

Adalimumab (ADA) is the third TNF inhibitor, after infliximab and etanercept. There are few data about its safety in pregnancy. For this reason, OTIS (Organization for Teratology Information Specialists) refers pregnant enrolled in a prospective study about ADA therapy.

They find out that the incidence of sponta-

Drug	Use in pregnancy	Use during nursing	Possible side effects
Sulfasalazine	SAFE	SAFE	Acid folic deficiency
Mesalamine	SAFE till 3g/die	SAFE	Gastrointest. symptoms
Metronidazole	SAFE after I trimester	CONTRAINDICATED	Preterm delivery
Fluoroquinolones	SAFE at lower doses	CONTRAINDICATED	Joint injuries
Tetracyclines	FORBIDDEN	FORBIDDEN	Fetal musculoskeletal dysfunctions and teeth discoloration
Sulfonamides	FORBIDDEN	FORBIDDEN	Cleft palate
Prednisone	Carefully, it crosses the placenta	Only during relapses	Preterm births, cleft lip or palate
Thiopurines	Well tolerated	SAFE	Ectopic pregnancy, preterm deliveries, spontaneous abortion
Cyclosporines	Carefully, it can cause teratogenic effects	FORBIDDEN	Spontaneous abortion
Tacrolimus	Not safe	Not safe	Preterm delivery
Methotrexate	CONTRAINDICATED	CONTRAINDICATED	Chromosomal abnormalities

**Table 3:** Main Drugs in Crohn Disease - Contraindications.

neous abortions, stillbirths, congenital abnormalities and preterm deliveries are similar for both groups (patients and controls). ADA probably crosses the placental barrier on third trimester. Generally ADA assayed during breastfeeding.

The incidence of inflammatory bowel disease (IBD) is highest during the peak reproductive years, so we have several cases of Crohn's Disease during pregnancy<sup>(20)</sup>.

Infertility rate in inactive CD is similar to the infertility rate of general population but, certainly, active disease decreases fertility.

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