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Original Article

Surgery due to Inflammatory Bowel Disease During Pregnancy: Mothers and Offspring Outcomes From an ECCO Confer Multicentre Case Series [Scar Study]

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Summary

Aims: i] To evaluate the evolution of pregnancies and offspring after inflammatory bowel disease [IBD] surgery during pregnancy; and ii] to describe the indications, the surgical techniques, and the frequency of caesarean section concomitant with surgery.

Methods: Patients operated on due to IBD during pregnancy after 1998 were included. Participating clinicians were asked to review their databases to identify cases. Data on patients' demographics, IBD characteristics, medical treatments, IBD activity, pregnancy outcomes, surgery, delivery, and foetal and maternal outcomes, were recorded.

Results: In all, 44 IBD patients were included, of whom 75% had Crohn's disease; 18% of the surgeries were performed in the first trimester, 55% in the second, and 27% in the third trimester. One patient had complications during surgery, and 27% had postsurgical complications. No patient died. Of deliveries, 70% were carried out by caesarean section. There were 40 newborns alive. There were four miscarriages/stillbirths [one in the first, two in the second, and one in the third trimester]; two occurred during surgery, and another two occurred 2 weeks after surgery; 14% of the surgeries during the second trimester and 64% of those in the third trimester ended up with a simultaneous caesarean section or vaginal delivery. Of the 40 newborns, 61% were premature and 47% had low birth weight; 42% of newborns needed hospitalisation [25% in the intensive care unit].

Conclusions: IBD surgery during pregnancy remains an extremely serious situation. Therefore, surgical management should be performed in a multidisciplinary team, involving gastroenterologists, colorectal surgeons, obstetricians, and neonatal specialists.

Key Words: Inflammatory bowel disease; Crohn's disease; ulcerative colitis; pregnancy; gestation; surgery

1. Introduction

Inflammatory bowel disease [IBD] commonly affects patients during their reproductive years. Disease activity is the main factor negatively affecting pregnancy outcome. Therefore, maintaining remission during conception and pregnancy is of utmost importance.[1] The incidence of relapse during pregnancy ranges from 20% to 50%, being similar to that in non-pregnant patients. Such patients require intensive medical treatment. However, despite the increasing number of drugs in the therapeutic armamentarium of IBD, some patients fail to respond and surgical intervention is needed.[2–6]

In general, the indications for emergency surgery for IBD are the same for pregnant and non-pregnant women, namely, failed medical therapy, toxic megacolon, perforation and intractable haemorrhage. However, the decisions regarding timing, approach and the appropriateness of surgery are often challenging. There have been few published reports on IBD surgery during pregnancy, most likely due to low frequency and under-reporting.[7–11] In this respect, data on the outcomes of surgery due to IBD in pregnant patients are scarce, and primarily date back more than three decades ago, pre-dating the use of biologic therapy, minimally invasive surgery and current perioperative management and support.[7]

In this exceptional clinical situation in which experience is very limited and under-reported, it is crucial to make a collaborative effort to systematically record all cases of surgery in patients with IBD during pregnancy. Therefore, our primary aim was to evaluate the evolution of pregnancies and offspring after IBD surgery. Our secondary aims were to describe the indications for surgery in these patients and the surgical techniques used, the complications during pregnancy, surgery and delivery, and in the offspring.

2. Methods

2.1. Study design

A retrospective, multicentre, non-interventional study was conducted to investigate maternal and foetal outcomes of pregnancies in IBD patients who underwent IBD surgery during gestation. The patients included in this study had been diagnosed with IBD and followed up in a specialised IBD care setting. Clinicians were asked to proactively review hospital databases to identify patients who met the inclusion criteria. In order to make it more homogeneous, the inclusion was limited to cases that had occurred since 1998, when the first biologic agent was approved for IBD treatment. Information available in the medical records was included in the electronic data collection file. Every patient who met the criteria in each participating centre was included. The study was approved by the Ethics Committee of Clinical Research of Hospital Universitario de La Princesa [Madrid, Spain].

The study was approved by ECCO [European Crohn's and Colitis Organisation] COllaborative Network For Exceptionally Rare Case Reports [CONFER], which is an initiative to identify, assemble, and report together rare IBD cases of clinical relevance, which are otherwise seldom reported. By joining forces with the many members and supporters of ECCO, a joint report of all similar rare cases can result in a large case series that will advance our knowledge about these uncommon patients.

2.2. Study population

Patient diagnosed with IBD (Crohn's disease [CD], ulcerative colitis [UC], or non-classified IBD] before surgery or at the time of surgery, and operated on due to IBD [any kind of surgery] during pregnancy from 1998, were included. Patients who gave birth (vaginally or by caesarean section [C-section]) at the time of IBD surgery [both interventions performed during the same admission] were also eligible. Patients operated on during puerperium were excluded from this study.

2.3. Data collection

Only available data, obtained as part of the patient's usual care, were collected. Data collected included demographics, IBD characteristics, obstetric history, previous treatment for IBD including surgery, date of conception, disease activity at conception and in each trimester of gestation, medical treatment for IBD during pregnancy, complementary examinations during pregnancy, date of surgery, indication and type of surgery, maternal and foetal complications during surgery, maternal and foetal complications during the postoperative period, date of delivery, type of delivery, maternal complications at delivery, newborn's weight, newborn's complications at birth and during the perinatal period, miscarriages and stillbirths.

2.4. Statistical analysis

For categorical variables, percentages were calculated. The descriptive analysis of quantitative variables calculated the mean and standard deviation [SD], or the median and interquartile range [IQR], depending on whether they were normally distributed or not. In the univariate analysis, categorical variables were compared using the chi square [χ^2] test, and quantitative variables using the appropriate test.

3. Results

3.1. Study population

A total of 44 patients were included of whom seven [16%] were diagnosed with IBD during pregnancy [two during the first trimester, three during the second trimester, and two during the third trimester of gestation]. Mean age at diagnosis was 25 years [SD = 6 years]. Main characteristics of the study population are summarised in Table 1.

Thirteen patients [30%] had comorbidities. With respect to toxic habits, nine patients [20.5%] were smokers during pregnancy and no one consumed alcoholic drinks or drugs of abuse. Seven [16%] patients had family history of IBD. Only one father had a relevant comorbidity [glycerol kinase deficiency, X-linked form of adrenal insufficiency].

With respect to IBD characteristics, 33 patients [75%] had CD, 12 [36%] had ileal, and 14 [42%] ileocolonic location. The majority of CD patients had complicated behaviour: 33% stricturing and 52% fistulising; nine CD patients [24%] had perianal disease. A total of 10 patients [23%] had UC; of them, nine [82%] had extensive colitis. A total of 12 patients [27%] had extraintestinal manifestations, peripheral arthropathy and erythema nodosum being the most frequents.

Overall, prior to conception 27 patients [59%] had been treated with systemic steroids, 28 [64%] with thiopurines, three [7%] with methotrexate, one [2%] with tofacitinib, and one [2%] with cyclosporine. In addition, 28 patients [64%] had been treated with biologic agents.

Table 1. Patients' characteristics.

Age at IBD diagnosis, years [mean, SD]	25 [6]
Time from IBD diagnosis to pregnancy, months [mean, SD]	69 [62]
Age at conception, years [mean, SD]	31 [5]
Diagnosis of IBD during pregnancy, *n* [%]	7 [16]
Family history of IBD, *n* [%]	7 [16]
Comorbidities, *n* [%][a]	13 [30]
Extraintestinal manifestations, *n* [%]	12 [27]
Previous surgery due to IBD, *n* [%]	15 [34]
Previous pregnancies, *n* [%]	24 [55]
IBD type (*n* [%])	
Crohn's disease, n [%]	33 [75]
L1	12 [36]
L2	7 [21]
L3	14 [43]
B1	5 [15]
B2	11 [33]
B3	17 [51]
Perianal disease	9 [24]
Ulcerative colitis, *n* [%]	10 [23]
Extensive colitis	9 [90]
Left-sided colitis	1 [10]
IBD unclassified, *n* [%]	1 [2]
Previous treatments for IBD, *n* [%]	
Thiopurines	28 [64]
Methotrexate	3 [7]
Biologics	28 [64]

IBD, inflammatory bowel disease; SD, standard deviation; *n*, number of patients
[a]1 [2%] had arterial hypertension, 1 [2%] diabetes mellitus, 1 [2%] thyroid disease, 1 [2%] allergy, and 3 [7%] asthma.

3.2. Medical management of IBD during pregnancy

The vast majority of pregnancies occurred spontaneously, as only one [2%] occurred after *in vitro* fertilisation. All pregnancies were singleton. Eighteen patients [41%] had active disease at conception, 25 [57%] at the first trimester, 32 [73%] at the second trimester, and 18 [41%] at the third trimester of gestation. Several examinations were performed during pregnancy, without complications [Figure 1]. Of note, six patients [14%] underwent colonoscopy, 14 [32%] sigmoidoscopy, and 18 [41%] magnetic resonance imaging. Medications received during pregnancy are summarised in Figure 1: 27 patients were exposed to steroids, 10 [23%] and 25 [57%] to biologic agents [11 to infliximab, 10 to adalimumab, two to certolizumab, two to vedolizumab, and two to ustekinumab]. Four patients needed to be admitted to the hospital for complications other than IBD: one hyperemesis, one gallstones, one hyperkalaemia, and one viral intestinal infection.

3.3. Surgery indications and outcomes

Indications, characteristics, and outcomes of surgery are summarised in Figure 2. The majority of surgeries were performed in university hospitals [93%]. Most of them were emergency surgeries [77%]. Mean gestational age at surgery was 22 weeks [SD = 9 weeks]: 18% [*n* = 8] of the surgeries were performed during the first, 55% [*n* = 24] during the second, and 27% [*n* = 12] during the third trimester of gestation. The majority of surgeries were abdominal surgeries [*n* = 42, 95%], 59% [*n* = 26] by laparotomy, and an ostomy was performed in 57% [*n* = 25] of the patients [temporary in 92% of the cases].

The main indications for surgery were the onset of complications associated with stricturing or fistulising CD and severe flare of UC. In consequence, the most frequent types of surgeries were intestinal resection [*n* = 26, 59%], and colectomy/subtotal colectomy [*n* = 10, 23%].

Early induction of labour was performed in three [12%] out of 24 women operated on in the second trimester of gestation, and in seven [58%] out of 12 women who underwent surgery during the third trimester of gestation. Only one patient experienced a complication during surgery [haemoperitoneum]. The patient had haemorrhagic shock, was admitted to the intensive care unit, and the foetus died *in utero*. In addition, 12 patients [27%] had postsurgical complications, most frequently intraabdominal infection. No woman died.

There were four foetal losses [11%] in our cohort, two of them during surgery and two others during the postoperative period. One patient underwent subtotal colectomy by laparotomy at Week 18 of gestation, due to acute severe UC flare, which caused a septic shock, and the foetus was lost during the procedure. Another patient with CD underwent surgery by laparoscopy at Week 39 of gestation due to intestinal obstruction; the patient suffered a haemoperitoneum and a haemorrhagic shock, and the foetus was lost during the surgical intervention. The third patient underwent urgent surgery due to acute severe UC at Week 16 of gestation [a subtotal colectomy by laparotomy]; the patient developed an abdominal abscess in the postoperative period, which led to infection of the amniotic fluid and caused miscarriage at Week 18 of gestation. Finally, the fourth patient underwent

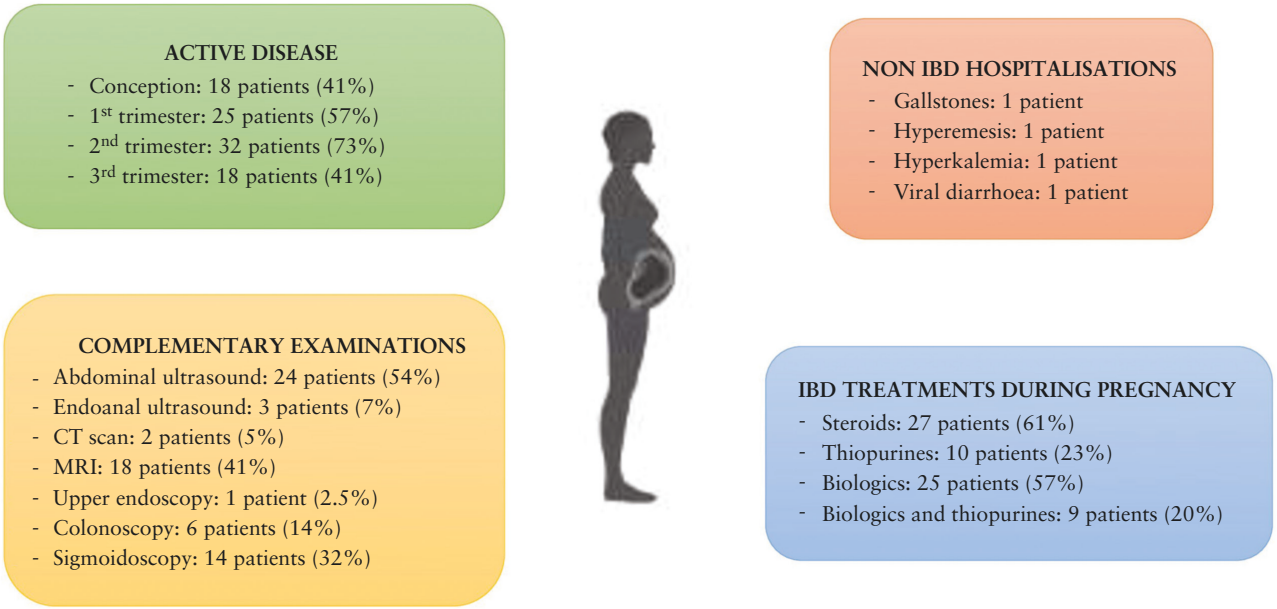

Figure 1. Inflammatory bowel disease [IBD] activity, complementary examinations during pregnancy, and treatments during pregnancy.

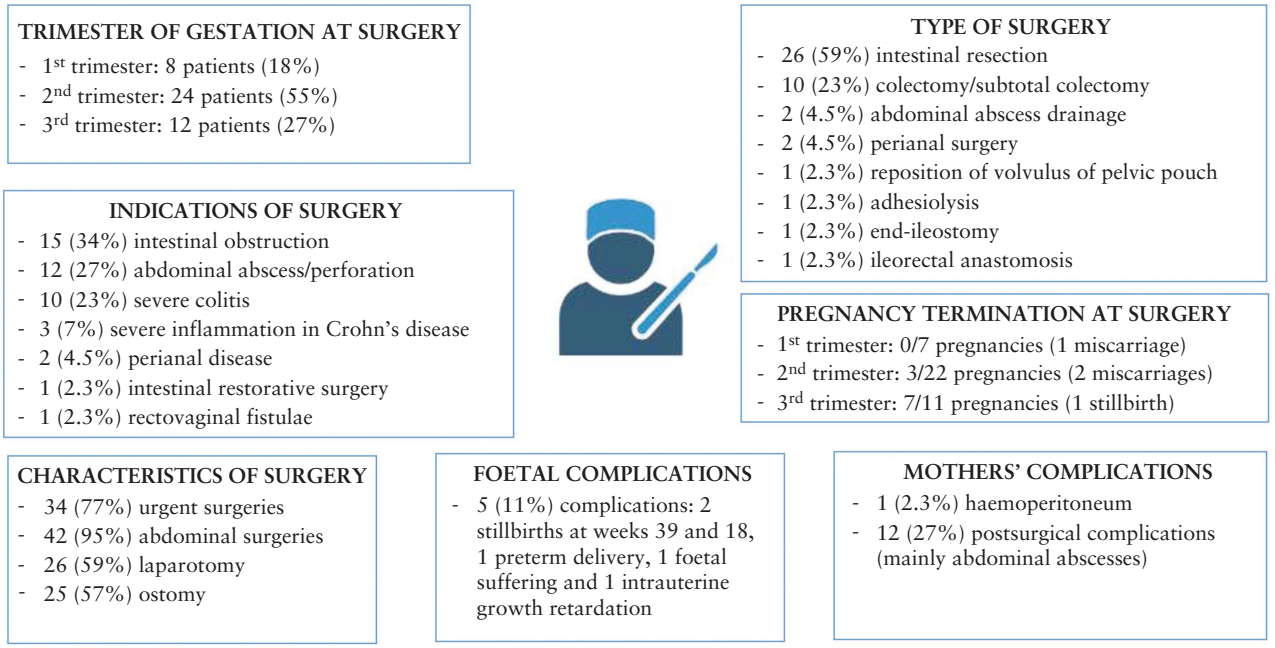

Figure 2. Indications, characteristics and outcomes of surgery due to inflammatory bowel disease during pregnancy.

subtotal colectomy by laparoscopy due to acute severe UC flare at Week 10 of gestation, and suffered a miscarriage 2 weeks later.

3.4. Delivery and newborn's outcomes

There were 40 [90%] live-born children and four miscarriages/stillbirths [one in the first, two in the second, and one in the third trimester] [Figure 3]. Mean time of gestation at delivery was 36 weeks [SD = 5 weeks]. In 15 patients [37.5%], labour started spontaneously, whereas it was induced in 28 [62.5%] cases: 32.5% programmed and 30% urgent induction of labour. Reasons for urgent induction of labour were: IBD complications in five cases, infection in two, increased labour and cervical shortening in two, abnormal cardiotocographic pattern in two, and preeclampsia in one patient. With respect to programmed induction of labour, the main reason was the presence of IBD complications. Three women had complications during delivery: two had infections, and one received intravenous antibiotics due to active perianal disease. Of note, 70% of deliveries were by C-section.

A total of 25 newborns [61%] were premature, 19 [47%] had low birth weight and nine [22.5%] were small for gestational age. Seventeen babies [42%] had prolonged hospitalisation after birth for the following reasons: prematurity in

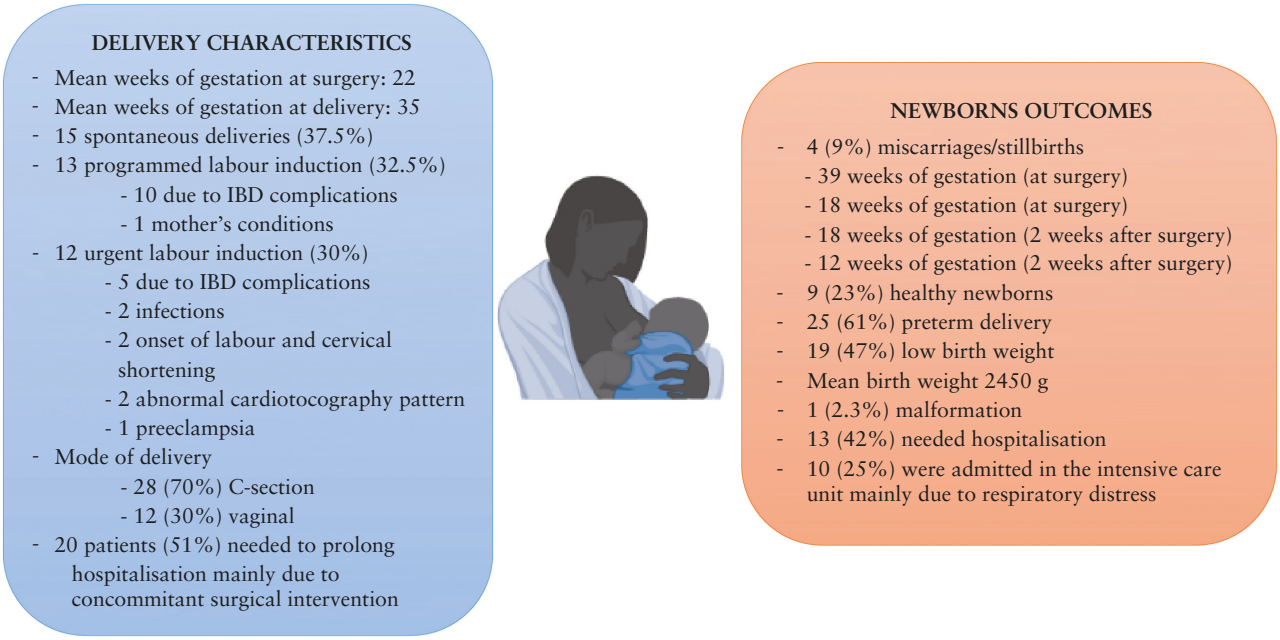

Figure 3. Characteristics and outcomes of delivery in patients operated on due to inflammatory bowel disease during pregnancy.

eight cases, respiratory distress, neonatal sepsis, patent ductus arteriosus and jaundice in one, neonatal abstinence syndrome due to opioid use during pregnancy in one, low birth weight in one, respiratory distress in one, newborn jaundice in one, need for nasogastric tube for feeding in one, management of the percutaneous endoscopic gastrostomy in one, and other reasons in two cases. Ten newborns were admitted to the intensive care unit, mainly due to respiratory distress.

One newborn born at Week 40 of gestation had malformations: cleft palate, ocular and skeletal malformations. The newborn had feeding difficulties and needed a percutaneous endoscopic gastrostomy. The mother had been treated with both infliximab and systemic steroids for 1 month before surgery [at Week 13 of gestation].

4. Discussion

To our knowledge, this is the largest reported series of women operated on due to IBD during pregnancy; in addition, it provides updated current information on the outcome of surgery in these patients in the era of biologic therapy. The main reasons for surgery were similar to those previously described [fistulising or stricturing complications in CD, or severe refractory flare in UC].[7,10] However in the present study, maternal and foetal outcomes such as miscarriage, stillbirth, and maternal/foetal death were markedly lower than previously described. This is most likely due to improved surgical techniques and medical and supporting care of the mother and the offspring. Of note, more than 80% of patients who underwent surgery during the second trimester, and about 40% of those who were operated on during the third trimester, managed to continue the pregnancy.

Literature on the outcome of surgery due to IBD in pregnant patients is very limited. Killeen *et al.* performed a systematic review of the available literature to identify optimal surgical management strategies for complicated and medically refractory IBD during pregnancy and the puerperium.[7] A total of 32 articles reporting 86 cases over a 60-year period [1950-2015] were finally included. A total of 56 patients had UC; among these there were eight maternal deaths [19%], which occurred before 1980, and 15 [35%] foetal deaths. With respect to CD, 20 patients were included; there was no maternal death and one miscarriage at Week 17 of gestation. In addition, Germain *et al.* recently published the largest series of pregnant patients operated due to CD in France.[10] A total of 15 cases operated on from 1992 to 2015 were included. Maternal mortality rate was 6.7% and neonatal mortality rate 9.1%. In addition, there were two miscarriages and two abortions. These cases were not included in this study.

Although there seemed to be an improvement in maternal, foetal, and perinatal mortality, the morbidity and the prevalence of complications were high and similar to those previously reported. The prevalence of maternal complications during surgery was low; however, one patient had haemoperitoneum and a haemorrhagic shock, which caused foetal death. In the postsurgical period, one in three patients experienced complications. With respect to delivery, in one-third of cases the labour had to be urgently induced due to the onset of maternal or foetal complications, resulting in one of the highest C-section rates reported among IBD patients.[12] Morbidity in the newborns were very high, and highlights the complexity associated with maternal surgery during pregnancy.

The risk of disease relapse in pregnant women with IBD is similar to that in non-pregnant patients. When the mother is in remission at conception, the remission is usually maintained during pregnancy; thus, planning conception when the patient is in remission is the best way of avoiding surgery.[13–15] On the contrary, when IBD is active at conception, the disease usually remains active or deteriorates in pregnancy.[13–15] In this sense, over 40% of the patients in our cohort had active IBD at conception, over 50% at the first trimester, over 70% at the second, and over 40% at the third trimester of gestation. The vast majority of pregnant IBD patients can be managed with medical treatment in case of disease relapse, and most of the medications are of low risk during pregnancy and

breastfeeding.[2–6] However, in cases of severe exacerbations refractory to medical treatment or complications, patients will have to undergo surgery. If this is the case, a multidisciplinary approach [including gastroenterologists, surgeons, obstetricians, and neonatologists, among others] should be taken, and ideally in a tertiary care facility. It is important that patients and physicians responsible for their care are aware that pregnant IBD patients should not stop the medication during pregnancy and the puerperium, to avoid disease relapse.

Some indications for surgery in pregnant IBD patients, such as perforation or complete obstruction, are clear. However, the indication for surgery due to medically refractory IBD is more challenging. Physical, psychological, and immunological changes in pregnancy, together with the reluctance of both the patient and the clinicians to operate owing to the fear of maternal and foetal morbidity and mortality, might delay surgery in some cases, which might lead to worse outcomes.

With respect to the difficulties in the assessment of disease severity, the pregnant uterus may make it difficult to perform an abdominal examination to rule out an acute abdomen. Haemodilution produces a decrease in haemoglobin and serum albumin. Heart rate in pregnant women is increased by 10%. In addition, clinical scoring systems for assessing the severity of IBD or the response to medical treatment, which include laboratory parameters affected by pregnancy and patients' weight, have not been validated in the pregnant population; thus they should be used with caution. In this scenario, objective tools for disease evaluation should be used. With respect to abdominal imaging, it is important for identifying complications associated with IBD during pregnancy. To avoid radiation, ultrasonography and magnetic resonance imaging without gadolinium are preferred over computed tomography [CT].[16–18]

It may be necessary to perform endoscopy either as part of the diagnostic work-up of IBD or to evaluate the activity of the disease and rule out causes of refractoriness. In our series, over one-third of patients underwent either colonoscopy or sigmoidoscopy, without complications. Data on the safety of endoscopy in pregnant patients with IBD are scarce. In general, it has been reported that both sigmoidoscopy and colonoscopy are of low risk in pregnant IBD patients and can guide the decision making process in a high proportion of patients.[19–21]

Some authors have suggested that surgery is of lowest risk when undertaken during the second trimester—there are higher risks of miscarriage in the first trimester and increased risks of maternal/foetal morbidity and mortality during the third trimester.[7,11] Nevertheless, and despite these considerations, once the indication for surgery is established, it should not be delayed, as this might be associated with worse outcomes.

With respect to the surgical approach, a minimally invasive approach is advocated by a number of authors from extrapolation from general surgical procedures during pregnancy or from surgery in non-pregnant IBD patients.[7,22–24] Laparoscopy is associated with smaller incisions, less adhesion formation, fewer complications, and quicker recovery than the open approach, and it would be the operative approach of choice mainly during the first and second trimesters, being technically more difficult during the third trimester. In the systematic review performed by Killien *et al.*, only two out of 86 patients were operated on by laparoscopic approach.[7] In the cohort published by Germain *et al.*, four out of 15 surgeries [27%] were performed by laparoscopy.[10] In our series, 40% of the procedures were performed by laparoscopy.

In previous series, many authors favour subtotal colectomy and end ileostomy in UC pregnant patients, regardless of the indication.[7] Some indications such as ischemia, perforation, or intractable bleeding might require colectomy; however, removing the rectum is not without risk to the mother and the foetus. If a major haemorrhage occurs from the engorged pelvic venous plexus during a surgery involving the rectum, it may even be necessary to perform an emergency hysterectomy. Furthermore, dehiscence of a close rectal stump also has devastating consequences. With respect to CD, the preferred surgical approach is influenced by the type of complication and disease location, besides factors due to the pregnancy. Killeen and colleagues suggest exteriorisation of the bowel; primary anastomosis might be associated with anastomotic leakage or ongoing sepsis, which might cause foetal death.[7] In our series, an ostomy was performed in about 60% of the cases, similarly to data reported by Germain *et al.*[10]

In our study, there was one stillbirth at Wk 39 of gestation in a CD patient who underwent surgery by laparoscopy due to intestinal obstruction. The patient suffered a haemoperitoneum and a haemorrhagic shock, and the foetus was lost during the surgical intervention. Surgical and obstetrical management should consider maternal and foetal status; however during the third trimester of gestation, delivery by C-section before surgery might be preferred and should be discussed in a multidisciplinary team including the patient's opinion.

Two of the four miscarriages/stillbirths in our cohort occurred during surgery, and the other two occurred 2 weeks after surgery. Rasmussen *et al.* examined the association between non-obstetric abdominal surgery during pregnancy and birth outcomes, using data from the national Danish registries covering 1997-2015.[11] The absolute risk of miscarriage was stratified by time since surgery. Authors observed that for miscarriage, the risk was highest the first week after surgery and levelled out after 2 weeks. These findings suggest that stricter foetal monitoring should be done during the first 2 weeks after surgery, to detect complications as early as possible.

Our study has limitations mainly derived from its retrospective design. First, detailed information about surgical techniques was not available in most cases. Second, although the investigators were asked to make an effort to identify cases, we recognise that this could be difficult and could introduce bias into the study results. However these are very complicated and rare cases, which will have to continue to be followed up for IBD, so it is relatively straightforward to identify them. Although there could be a recall bias towards the more severe cases, our results indicate that the evolution during and after surgery, although still a complicated situation, is better than those previously described. Finally, most patients had been managed in referral/university centres with a wide experience in IBD treatment, capable of providing advanced supporting care to the patients in the perioperative period and to the neonates in the postpartum, which could bias the results.

Our study has several strengths: to our knowledge it is the largest series to date assessing the outcomes of surgery due to IBD during pregnancy. In addition, it is representative of what happens nowadays, allowing the extrapolation of the results

to our current population. Of note, all patients were operated on from 1998, a high proportion of patients were exposed to thiopurines and biologics, and 40% of the abdominal surgeries were performed by laparoscopy.

In conclusion, we have reported the largest series of patients operated on due to IBD during pregnancy. We have shown that although maternal and neonatal mortality seems to be lower than in previous decades, maternal and foetal morbidity is still high. These results emphasise the extreme complexity of this clinical situation and the importance of a multidisciplinary management where the indication of surgery, the surgical approach, the timings for surgery and delivery, and the perioperative, obstetric, and neonatal management are performed in the best possible conditions.

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Nothing to declare.

Conflict of Interest

MC has served as a speaker, as consultant, or has received research or education funding from MSD, Abbvie, Hospira, Pfizer, Takeda, Janssen, Ferring, Shire Pharmaceuticals, Dr Falk Pharma, Tillotts Pharma, Biogen and Gilead. GD received speaker fees from Novartis. MBA has served as a speaker, consultant and advisory member for, or has received research funding from MSD, AbbVie, Janssen, Kern Pharma, Celltrion, Takeda, Gillead, Celgene, Pfizer, Sandoz, Biogen, Fresenius, Ferring, Faes Farma, Dr Falk Pharma, Chiesi, Gebro Pharma, Adacyte and Vifor Pharma. NT reports personal fees from AbbVie, Falk Foundation, Janssen, and Takeda outside the submitted work. AB-GS reports consulting/advisory fees from Takeda, Janssen, Neopharm, Pfizer, and AbbVie; speaking and teaching fees from Takeda, Janssen, AbbVie, Neopharm, and Pfizer; and research support from Takeda and Janssen. JPG has served as a speaker, a consultant and advisory member for, or has received research funding from MSD, Abbvie, Pfizer, Kern Pharma, Biogen, Mylan, Takeda, Janssen, Roche, Sandoz, Celgene, Gilead, Ferring, Faes Farma, Shire Pharmaceuticals, Dr Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, and Vifor Pharma. TM has received speaker's honoraria from MSD, AbbVie, Egis, Goodwill Pharma, Takeda, Pfizer, and Teva. The rest of authors have nothing to declare.

Author Contributions

MC and JPG: study design, data collection, data analysis, data interpretation, writing the manuscript. Rest of authors: patient inclusion. All authors approved the final version of the manuscript.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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