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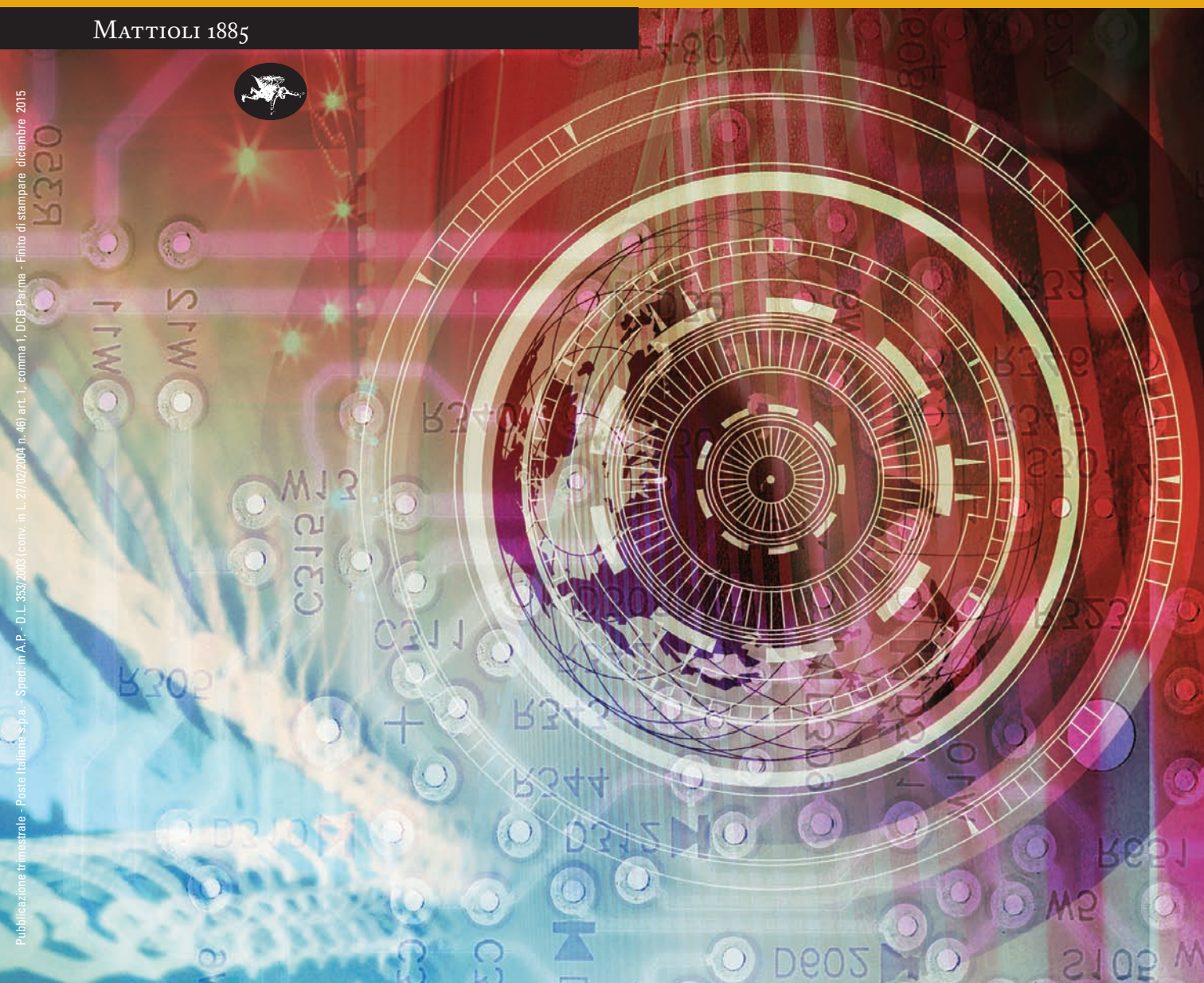

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Review

Inflammatory Bowel Disease (IBD) in pregnancy: analysis of the possible effects of the disease on the fetus and the newborn and therapeutic approaches

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Summary. The Inflammatory Bowel Diseases are a group of inflammatory diseases characterized by the presence of chronic inflammation, in the absence of infectious etiology. The two most well-known diseases in this group are: Crohn's disease (CD) and Ulcerative Colitis (UC). In cases where it is not possible to distinguish between CD and UC, it is called Indeterminate Colitis. Inflammatory Bowel Diseases (IBD) can affect women pregnant. The causes of IBD are unknown, and the clinical course of the disease is characterized by phases of activity and remission. UC is a chronic inflammation of the mucosa of the colon and involving predominantly the left colon and rectum. It is associated with presence of blood and mucus in the stool, diarrhea and anemia. Characteristically, CD involves entire gastrointestinal tract, from the mouth to the anus. In CD, the inflammatory infiltrate involves the entire intestinal wall. Clinically manifested by abdominal pain, diarrhea, loss of appetite and weight loss. The complications are stenosis , fistulas, abscesses, and perianal involvement. In IBD TNF-alpha and proinflammatory cytokines are overexpressed. The analysis of the scientific literature shows that fertility, in pregnant women suffering from IBD, is preserved. It shows slightly reduced for CD and ileo-anal pouch. Women with active disease at the time of conception have an increased risk of spontaneous abortion, preterm birth, with low birth weight and congenital malformations of the fetus. The indications for surgical treatment are the same as for non-pregnant women. The inactive disease or ileo-anal pouch is not a contraindication to spontaneous vaginal delivery, as is happens in the case of active colitis or perirectal fistulas or rectovaginal fistulas. Safe drugs during pregnancy are: 5-aminosalicylic acid (5-ASA), steroids, 6-mercaptopurine (6MP)/Azathioprine (AZA) and Infliximab. Contraindicated drugs are Methotrexate and Thalidomide. In conclusion, the expectations about pregnancy, in women affected of IBD, is similar to the general population, especially if the conception occurs in inactive phase of the disease.

Key words: Intestinal Bowel Diseases, ulcerative colitis, Crohn disease, pregnancy

[*] Arculeo Vincenza Maria, Marcello Noto and Giovanni Tomasello the first authorship

Introduction

Over the last 20 years, in industrialized countries, including Italy, a continuous increase in the incidence of CD has been registered. Epidemiological data show that this disease also affects women of childbearing age, especially among 20-25 years.

Today we know that the disease can occur at any age, even around 60-70 years. UC has an annual incidence of about 5-7 cases per 100,000 inhabitants. CD, however, has an annual incidence of 3-4 cases per 100,000 inhabitants (1).

UC typically involves the mucosa of the rectum and sigmoid colon. It can also spread and affect the entire colon. IBD-related mucosa alterations include: inflammation, oedema, and severe cases of erosions or ulcerations. The most common symptom is proctorragia or blood in the stools. Other symptoms are diarrhoea, the emission of mucus always associated with blood, urgency, tenesmus, abdominal pain in the lower abdomen. A constant blood loss can lead to severe anaemia (2). The clinical course of the disease is characterized by phases of remission, or acute phases with acute exacerbation of the clinical symptoms. In UC we can also have extraintestinal manifestations. Between these, the most frequent involve joints, skin, eye, also including sclerosing cholangitis (3, 4).

CD is a chronic inflammation that can affect any segment of the gastrointestinal tract, from mouth to anus. The most common location is in the ileum and colon. The inflammation involves the full-thickness intestinal wall. The disease was named after Dr. Burrill B. Crohn described it for the first time in 1932. The causes are not yet known and the disease is characterized by alternating phases of activity and remission. The most common symptoms are abdominal pain, often in the periumbilical and right upper quadrant, associated with diarrhoea. Frequently, loss of appetite and weight loss appear; fever may occur. In CD the intestinal wall is thickened and congested. Mucosal lesions have a segmental appearance; areas of inflamed mucosa are interspersed with areas of smooth mucosa. Mucosal ulcers may deepen in the intestinal wall and form the characteristic appearance of "cobblestones". The inflammation of the entire colonic wall, can lead to adhesions between the intestinal loops. These adhesions can correlate with the formation of colic fistulas (colo-cutaneous fistulas, colo-vescical fistulas, biliary-colonic fistula, etc...). The formation of scar tissue (for an excessive production and accumulation of collagens in fibrotic disease), leads to the formation of cicatricial stenoses of bowel loops. This situation predisposes to bowel obstruction and acute abdomen.

In CD (similarly to other IBD) extraintestinal manifestations which may involve different organs or systems can occur (Tab. 1).

The severity and characteristics of IBD extraintestinal manifestations depend on the extension and intensity of the inflammation, and the presence or absence of complications (5-7). The aetiology of IBD is still unknown; however, several etio-patgogenetic hypotheses have been reported. For CD, a viral origin has been suggested; some epidemiological data involve the measles virus. This virus, persisting in the intestinal endothelium after infection, induces an inflammatory response with a granulomatous vasculitis. The hypothesis of a bacterial etiology refers to the mycobacterium avium paratuberculosis, which is the causative agent of *'Johne's disease'*. This disease presents clinical symptoms very similar to CD (8, 9). Other studies have showed the association of CD with the presence of serum *anti-Saccharomyces Cerevisie* (10). Also, the genetic hypothesis has been carefully considered. Molecular biology has identified specific genetic mutations in IBD. More specifically, on the short arm of chromosome 16 a locus, called IBD1, which makes individuals susceptible to CD, has been identified. Other genes involved are the CARD15 (known as NOD2) and others located in chromosome 11 and 5 (11). The gene ATG16L1, recently discovered, seems to reduce macrophage response activity and favours bacterial invasion (12). However, not a single mutation appears to be respon-

Table 1. Common extraintestinal manifestations in IBD (5-7, 50)

Skin lesions	erytema nodosum, pyoderma gangrenosum
Orthopedic lesions	arthralgia, arthritis, sacro-ilitis, ankylosing spondylitis
Oral lesions	mucogingivitis, aphthous stomatitis, pyostomatitis vegetans
Ocular lesions	uveitis, episcleritis

sible for the onset of the disease, but rather there are many other predisposing factors. The incidence of the disease is higher in industrialized countries, particularly in urban areas and in smoking patients. Dietary habits appear to be one of the risk factors of the disease; especially, for those rich in fat and refined sugar (13-14). Similar to CD, UC has a genetic predisposition too. (15, 16).

IBD in pregnancy

During pregnancy, there are mild to moderate types of IBD, which are characterized by long periods of remission, and types with a more aggressive evolution, with complications and extra-intestinal manifestations. Nevertheless, in pregnancy is high the percentage of patients who undergo surgery, as a result of the severe disease. Many are the difficulties related to the management of IBD during pregnancy. For the treatment of a pregnant with IBD, a close collaboration of gastroenterologist and gynaecologist should be mandatory.

The most important aspects to consider are:

- effect of IBD on pregnant;
- effect of pregnancy on IBD;
- effects of the disease on the foetus;
- medical or surgical treatment.

Family history of the pregnant woman is a crucial aspect in the management of the disease. In general, the risk of transmitting IBD to the offspring ranges from 5% to 10%. If both parents have IBD, the probability of manifesting the disease is 36%; this indicates the importance of genetic transmission (17). The fertility seems to be normal for UC and could be slightly decreased for CD. This may be related to the transmission of the inflammatory process in the ovaries and the fallopian tubes, or to the poor nutritional intake that accompanies the disease (18). In these patients, a decreased libido (but also in partner), related to complications of the disease (perianal pain, rectal vaginal fistula), could be recognized (18,19).

The *European Crohn's and Colitis Organization (ECCO)* has announced the publication of new guidelines regarding pregnancy and related problems (39). Recently, the international scientific literature has experienced an increase in scientific papers published on the subject. We report the Israeli multicenter study conducted by *Dotan* (40) involving 159 mothers with IBD compared with 175 healthy mothers. Data collected from this study are summarized as follows:

a) IBD patients conduct a single pregnancy more frequently than controls ($p = 0.028$). One possible explanation for this phenomenon is the reluctance of the patients suffering from a such disabling condition to become pregnant. These data are also confirmed by studies conducted by Mañosa et al. (41) and Selinger et al. (42), where 75% of IBD female patients fear of transmitting the disease to their children, and 30% of them decide not to get pregnant.

b) Mothers with IBD are less prone to breastfeed their children, especially when compared to healthy ones ($p < 0.0001$). In a recent multicenter study, conducted by de Meij et al. (43), only 9 out of 30 children of IBD mothers were breast-fed. *ECCO 2010* guidelines (39) showed a lower birth weight for those children of IBD female patients ($p = 0.007$). These data were also confirmed by a study published by Bortoli et al. in 2011 (44).

c) The children of mothers with IBD have a greater incidence of congenital anomalies (especially limb deformities) ($p < 0.035$). Although some meta-analyzes have not evidenced a real correlation between IBD and the development of congenital anomalies, the presence of limb deformity is reported by several publications, including the above cited ECCO 2010 guidelines (39).

d) Those children of IBD mothers show major problems in neuromotor development (motor delay, $p = 0.03$) (39).

e) During pregnancy, a recurrence of disease was registered in 30% of cases, occurring more frequently in the first quarter (45%). Pregnancy, itself, does not increase the risk of recurrence, if conception occurs in clinical remission (39).

f) Children born from mothers with active IBD, are more likely premature and show a lower body weight. This data was registered especially in those patients treated with steroids, and decreased in those treated with salicylates or immunosuppressants. The multicenter studies conducted by Meij et al. (43) and by Casanova et al. (45) showed that Thiopurines are

a safe drug during pregnancy. However, the study of Jharap et al. (46) reported, in 30 pregnant women exposed to thiopurines, an altered metabolism of these drugs. Both values returned normal after childbirth. Interestingly, Marchioni et al. (47) demonstrated an uncertain safety of anti-TNFα drugs during pregnancy. Similarly, several authors recommend to suspend anti-TNFα treatment shortly before delivery. Furtermore, the study of Zelinková et al. (48) showed, in 31 pregnant who have discontinued therapy before the birth, persistent anti-TNFα drug levels in the umbilical cord blood of the foetus. We are waiting for the results of the the ongoing prospective study named "*PIANO*" (49), involving 1000 pregnant women, in which patients have been exposed immunosuppressive and biological drugs. Pregnant patients with IBD, in a state of remission or mild disease have the same risk of spontaneous abortion of the general population (20). Women with IBD in an active phase at the time of conception have a higher risk of spontaneous abortion. The risk of foetal death, during pregnancy, or neonatal death, increases proportionally with the increase of disease activity (60% risk in severe CD, 20-40% risk in severe UC, 60% of risk in fulminant UC). Scientific literature shows that a non-active disease at conception is recommended to reduce the risk of foetal complications, such as preterm birth and low birth weight (21). Literature does not reveal specific details regarding the type of delivery. To date, gynaecologists prefer a natural delivery, if the disease is in a phase of remission, whereas in a case of active disease (particularly if complicated with perianal disease), they recommend cesarean delivery (23, 24).

Effects of pregancy on IDB

During pregnancy, no significant differences were demonstrated in the course of CD and UC, and the risk of exacerbation does not seem to increase. Some clinical trials have shown that the development of bowel disease during pregnancy does not increase the number of relapses, compared to control population. However, if the disease is present in the active phase at the time of conception, it increases the risk of persistent symptoms and recurrence of 60-70%, especially in the first quarter of pregnancy (26, 27). This could be due to the discontinuation of drug therapy. There is no certainty that voluntary abortion leads to a decrease of relapses (27). The prognosis of IBD that begins during pregnancy is not worse than others. Perhaps, this can be explained by the altered immune response of the pregnant, with and a greater immunological tolerance which could lead to a reduction of inflammatory processes (28).

Farmacological therapy of IBD during pregnancy

There are numerous reports present in the literature about the safety of drug therapy during pregnancy (30). The treatment of IBD in pregnant women was based, from the mid-fifties to the mid-nineties, mainly on the use of glucocorticosteroids. Subsequently, these drugs were associated to immunosuppressants (mainly AZA) and antibiotics.

Corticosteroids

Corticosteroids have been used for the treatment of various diseases during pregnancy (asthma, rheumatoid arthritis). The use of corticosteroids did not show an increased risk of foetal malformations. In a study conducted by Fraser et al. (35), involving 531 pregnant women, the patients received doses of corticosteroids in different periods of their pregnancy. Premature births, spontaneous abortions and defects in mental development were nor observed. When necessary, corticosteroids can be administered safely to control active disease during pregnancy. There is the possibility of adrenal gland suppression among infants of mothers taking steroids. Therefore, the use of steroids more easily metabolized by the placenta, such as prednisone or prednisolone, is recommended.

5-Aminosalycilates

a) Mesalazine

Mesalazine is a safe drug during pregnancy. Its use is not a contraindication for breastfeeding as the percentage of drug that passes into breast milk is very low (32-33).

b) Sulfasalazine

Although there are occasional reports of congenital anomalies associated with the use of *sulfasalazine* in pregnancy, several studies have demonstrated its safety. Pregnant women treated with sulfasalazine should take at least 2 mg of folate supplementation per day, as sulfasalazine interferes with the normal folate metabolism (31).

Antibiotics

a) Metronidazole

Metronidazole is the antibiotic most widely used in IBD. However, the literature shows reports of fetal malformations, although studies have found no relationship between *metronidazole* during pregnancy and birth defects (29).

b) Ciprofloxacin

A review of the literature showed that the intake for a short period of ciprofloxacin in pregnancy is safe, although complications can occur such as premature birth (34).

Immunosuppressunts

a) Azathioprine/6-Mercaptopurine

Azathioprine passes into the fetal blood in an inactive form, therefore the fetus is not exposed to the effects of the substance. This makes possible its use during pregnancy, if indicated. In those cases of clinical remission, it is recommended to stop taking the drug before conception (34-36).

b) Methotrexate

Methotrexate is contraindicated during pregnancy. After its assumption, miscarriages in 40% of patients and fetal abnormalities, including spina bifida, in 30% of cases, have been reported (37).

c) Thalidomide

Thalidomide is contraindicated during pregnancy. After its administration, spontaneous abortion, fetal death in 30% of pregnancies, and cases of fetal limb malformation (phocomelia), have been reported (37).

d) Cyclosporine

Cyclosporine is the most used immunosuppressant during pregnancy. This drug can be used in severe or fulminant ulcerative colitis, for the purpose of delay or avoid surgery. *Mosckoviz DN* et al. conducted a study (30) on the use of cyclosporine in IBD in the acute phase, and noted the possibility of spontaneous abortions but no congenital anomaly or nephrotoxicity.

e) Infliximab

Infliximab is a chimeric monoclonal antibody (human/murine), which acts blocking selectively the action of TNF-α, one of the most powerful pro-inflammatory and cytolesive cytokine. Several studies have demonstrated that the intravenous infusion of infliximab in patients suffering from CD, determines a regression of inflammation in a statistically significant number of patient, in comparison with placebo group (27). Infliximab side effects on pregnancy are not completely known. Spontaneous abortion or even Fallot's tetralogy have been described (38).

Conclusions

There are no statistical significant differences, in terms of complications or disease recurrence during pregnancy or deliver, in IBD patients in comparison with general population. Importantly, miscarriages or premature births likely depends on disease activity at the time of conception. The standard treatment with steroids and 5-ASA has no harmful effects on the foetus, and the maintenance of clinical remission is the most important factor for a regular course of pregnancy and childbirth.

We can summarize the practical recommendations as follows:

1. a new pregnancy should start during an in inactive phase of the disease;
2. during pregnancy, a standard therapy with salazopyrine or 5ASA should be continued, increasing their dosages or adding systemic steroid therapy in case of disease relapse;
3. is useful to program a tight control obstetrician in the third quarter;
4. the mode of delivery depend on the activity of the disease but especially by the perineal obstetric conditions.

References

1. Hanauer A, Stephen B. Inflammatory bowel disease. New England Journal of Medicine 2006; 334: 841-48.
2. Sinagra E, Tomasello G, Raimondo D, Rossi F, Facella T, Cappello F, Damiani P, Abruzzo A, Bruno A, Palumbo VD, Cosentino L, Cottone M, Criscuoli V, Noto M, Lo Monte AI. Nutrition,malnutrition and dietary interventions in inflammatory bowel disease. Progress in Nutrition 2014;16(2):79-89.
3. A. Geraci, G. Tomasello, P. Damiani, G. Mazzoccato, L. Marinato, M. Gasparo. Bone loss in Inflammatory Bowel disease:our multicentric study. Endocrinology Studies 2011: vol.1:e3:10-13.
4. A.Geraci, G. Tomasello, S. Pasqualino Sabetta. Orthopaedic experience on inflammatory bowel diesease (Lesnjowski-Crohn's disease and ulcerative colitis). Ortopedia Traumatologia Rehabilitacia 2010;12(5):430-34.
5. G. Margiotta, A. Sanfilippo, FM Accardo, P. Damiani, A. Geraci, G. Tomasello. Chronic Inflammatory Bowel Disease in patients with orthopedic manifestation. Comparison with the data reported in international literauture". Euromediterranean Biomedical Journal 2012,7(7):33-38.
6. G. Margiotta, A. Sanfilippo, M.F. Accardo, P. Damiani, A.Geraci, G. Tomasello. Bone and joint manifestations in patients affected by inflammatory bowel disease. Capsula Eburnea 2011; 6(15):68-71.
7. G. Tomasello, A. Geraci, A. Sanfilippo, P. Damiani, S. Termine, R. M. Maritano, A. M. Maiorana, M. D'Arienzo. Rheumatic pathologies in subjects with inflammatory bowel disease. Capsula Eburnea 2010;5(24):142-46.
8. Naser SA, Collins MT. Debate on the lack of evidence of Mycobacterium avium subsp.paratuberculosis in Crohn's disease.Inflamm Bowel Dis 2005; 11: 1123.
9. G. Tomasello, M.Bellavia, V.D. Palumbo, M.C. Gioviale, P. Damiani, A.I. Lo Monte. From gut microflora imbalance to mycobacteria infection: is there a relationship with chronic intestinal inflammatory diseases? Ann Ital Chir 2011;82:361-368.
10. Giaffer MH, Clark A, Holdsworth CD. Antibodies to Saccharomyces cerevisiae in patients with Crohn's disease and their possible pathogenic importance. Inflamm Bowel Dis 1992; 33: 1071-5
11. Ogura Y, Bonen DK, Inohara N. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature 2001; 411: 603-6.
12. Prescott NJ, Fisher SA, Franke A, Hampe J, Onnie CM, Soars D, Bagnall R, Mirza MM, Sanderson J, Forbes A, Mansfield JC, Lewis CM, Schreiber S, Mathew CG. A nonsynonymous SNP in ATG16L1 predisposes to ileal Crohn's disease and is independent of CARD15 and IBD5. Gastroenterology 2007; 132: 1665-71.
13. Sakamoto N, Kono S, Wakai K. Dietary risk factors for inflammatory bowel disease: a multicenter case-control study in Japan. Inflamm Bowel Dis 2005; 11: 154-63.
14. Tralongo P, Tomasello G, Sinagra E, Damiani P, Leone A, Palumbo VD, Giammanco M, Di Majo D, Damiani F, Abruzzo A, Bruno A, Cassata G, Cicero L, Noto M, Tomasello R, Lo Monte AI. The role of butyric acid as a protective agent against infiammatori bowel disease. Euromediterranean Biomedical Journal, 2014;9(4):24-35.
15. Baumgart DC, Carding SF. Inflammatory bowel disease: cause and immunobiology. Lancet. 2007 May 12; 369(9573): 1641-57. Review.
16. Cho JH, Nicolae DL, Ramos R, Fields CT, Rabenau K, Corradino S, Brant SR, Espinosa R, LeBeau M, Hanauer SB, Bodzin J, Bonen DK. Linkage and linkage disequilibrium in chromosome band 1p36 in American Chaldeans with inflammatory bowel disease. Hum Mol Genet 2000; 9: 1425-32.
17. Orholm M, Binder V, Sorensen TI, Rasmussen LP, Kyvik KO. Concordance of inflammatory bowel disease among Danish twins. Results of a nationwide study. Scand J Gastroenterol 2000; 35: 1075-81.
18. Friedman S. Management of inflammatory bowel disease during pregnancy and nursing. Semin Gastrointest Dis 2001; 12: 245-52.
19. Munkholm P. Pregnancy, fertility, and disease course in patients with Crohn's disease and ulcerative colitis. Eur J Intern Med 2000; 11: 215-21.
20. Heetun ZS, Byrnes C, Neary P, O'Morain C. Reproduction in the patient with inflammatory bowel disease. Aliment Pharmacol Ther 2007; 26: 513-35.
21. Duvnjak M, Lerotìc I, Tomasìc V, Pavic T, Virovìc L. Inflammtory bowel disease and pregnancy. Lijec Vjesn 2006; 128: 48-55pag. 820;
22. Sonntag B, Stolze B, Heinecke A, Luegering A, Heidemann J, lebiedz P, Rijcken E, Domschke W, Kucharzik T, Maaser C. Preteterm birth but not mode of delivery is associated with an increased risk of developing inflammatory bowel disease later life. Infiamm Bowel Dis 2007; 13: 1385-90.
23. Dominitz JA, Young JC, Boyko EJ. Outcomes of infant born to mothers with inflammatory bowel disease: a population-based cohort study. Am J Gastroenterol 2002; 97: 641-8.
24. Beniada A, Benoist G, Maurel J, Dreyfus M. Inflammatory bowel disease and pregnancy: report of 76 cases and review of the literature. J Gynecol Obstet Boil Reprod 2005; 34: 581-8.
25. Mahadevan U, Sandborn WJ, Li DK, Hakimian S, Kane S, Corley DA. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. Gastroenterology 2007; 133: 1106-12.
26. Kane S. Inflammatory bowel disease in pregnancy. Gastroenterol Clin North Am 2003; 32: 232-40.
27. Riis L, Vind I, Politi P, Wolters F, Vermeire S, Tsianos E, Freitas J, Mouzas I, Ruiz Ochoa V, O'Morain C, Odes S, Binder V, Moum B, Stockbrugger R, Langholz E, Munkholm P, European Collaborative study group on Inflammatory Bowel Disease. Does pregnancy change the disease course? A study in European cohort of patients with inflammatory bowel disease 2006; 101: 1539-45.

28. Kane S, Kisiel J, Shih L, Hanauer S. HLA disparity determines disease activity through pregnancy in women with inflammatory bowel disease. Am Gastroenterol 2004; 99: 1523-6
29. Farouk R, Pemberton JH, Wolff BG. Functional outcomes after ileal-anal anastomosis for chronic ulcerative colitis. Dis Colon Rectum 2000; 231: 919-26.
30. Mosckoviz DN, Bodian C, Chapman ML, Marion JF, Rubin PH, Scherl E, Present DH. The effect on the fetus of medications used to treat pregnant inflammatory bowel disease patient. Am J Gastroenterol 2004; 99: 656-61.
31. Norgard B, Zeizel E, Rockenbauer M. Population based case control study of the safety of sulfalazine use during pregnancy. Aliment Pharmacol Ther 2001; 15: 483-6.
32. Diav Citrin O. The safety of mesalazine in human pregnancy: a prospective controlled cohort study. Gastroenterology 1998; 114: 23-8;
33. Marteau P. Foetal outcome in women with inflammatory bowel disease treated during pregnancy with oral mesalazine microgranules. Aliment Pharmacol Ther 1998; 12: 1101-8.
34. Ferrero S, Ragni N. Inflammatory bowel disease: management issues during pregnancy. Arch Gynecol Obstet 2004; 270: 79-85.
35. Fraser FC. Teratogenic potential of corticosteroid in humans. Teratology 1995; 51: 45-6.
36. Nielsen KO, Vainer B, Rask-Madsen J. Review article: the treatment of inflammatory bowel disease with 6-mercaptopurine or azathioprine. Aliment Pharmacol Ther 2001; 15: 1699-78.
37. Mottet C, Juillerat P, Gonvers JJ, Froehlich F, Burnand B, Vader JP, Michetti P, Felley C. Pregnancy and Crohn's disease. Digestion 2005; 71: 54-61.
38. Mahadevan U, Kane S, Sandborn WJ. Intentional infliximab use during pregnancy for induction or maintenace of remission in Crohn's disease. Alimentary Pharmacology e therapeutics 2005; 21: 733-38.
39. van der Woude J, Kolacek S, Dotan I, et al. European evidenced-based consensus on reproduction in inflammatory bowel disease. J Crohns Colitis 2010;4:493-510.
40. Dotan I, Alper A, Rachmilewitz D, et al. Maternal inflammatory bowel disease has short and long-term effects on the health of their offspring: A multicenter study in Israel. J Crohns Colitis 2013;7:542-50.
41. Mañosa M, Navarro-Llavat M, Marín L, et al. Fecundity, pregnancy outcomes, and breastfeeding in patients with inflammatory bowel disease: a large cohort survey. Scand J Gastroenterol 2013;48:427-32.
42. Selinger CP, Eaden J, Selby W, et al. Inflammatory bowel disease and pregnancy: Lack of knowledge is associated with negative views. J Crohns Colitis 2013;7:e206-13.
43. de Meij TG, Jharap B, Kneepkens CM, et al. Long-term follow-up of children exposed intrauterine to maternal thiopurine therapy during pregnancy in females with inflammatory bowel disease. Aliment Pharmacol Ther 2013;38:38-43.
44. Bortoli A, Pedersen N, Duricova D et al. Pregnancy outcome in inflammatory bowel disease: prospective European case-control ECCO-EpiCom study, 2003-2006. Aliment Pharmacol Ther 2011;34:724-734.
45. Casanova MJ, Chaparro M, Domènech E, et al. Safety of thiopurines and anti-TNF-α drugs during pregnancy in patients with inflammatory bowel disease. Am J Gastroenterol 2013;108:433-40.
46. Jharap B, de Boer NK, Stokkers P, et al. Intrauterine exposure and pharmacology of conventional thiopurine therapy in pregnant patients with inflammatory bowel disease. Gut 2013 Feb 19. [Epub ahead of print]).
47. Marchioni RM, Lichtenstein GR. Tumor necrosis factor-α inhibitor therapy and fetal risk: A systematic literature review. World J Gastroenterol 2013;19:2591-602.
48. Zelinkova Z, van der Ent C, Bruin KF, et al. Effects of discontinuing anti-tumor necrosis factor therapy during pregnancy on the course of inflammatory bowel disease and neonatal exposure. Clin Gastroenterol Hepatol 2013;11: 318-21.
49. Mahadevan U, Martin C, Sandler RS et al. PIANO: a 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy; Gastroenterology 2012;142(5 Suppl.:S149).
50. Lankarani KB, Sivandzadeh GR, Hassanpour S. Oral manifestation in inflammatory bowel disease: a review. World J Gastroenterol. 2013 Dec 14;19(46):8571-9

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