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Advances in Research on the Incidence, Risk and Treatment of Crohn's Disease during Pregnancy

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Abstract

Crohn's disease is an intestinal inflammatory disease of unknown cause, which is clinically divided into acute phase, subacute phase, and chronic phase. The disease symptoms can invade the entire digestive tract, and the most typical lesions are concentrated at the end of the ileum and its adjacent colon. The main manifestations of patients are diarrhea, abdominal pain, fistulas and perforating inflammation, most of which are in segmental and asymmetrical distribution. The symptoms are characterized by repeated attacks and alternating relief. There is no treatment plan to completely cure Crohn's disease. During pregnancy, the various systems of women's bodies have undergone tremendous changes due to the gestation of the fetus, so various complications are prone to occur, which is an important critical period for women of childbearing age. In addition, there are many contraindications to medication during pregnancy, so the treatment of ulcerative colitis during pregnancy has become a difficult problem. Therefore, urgent research for understanding the incidence, risk and treatment of Crohn's disease during pregnancy based on the existing evidence in practice diagnosis and treatment as well as the pregnancy safety information of relevant therapeutic drugs is required. Such research will help us accurately evaluate the corresponding diagnosis and treatment methods during pregnancy. Moreover, it can provide the best advice and management for patients with Crohn's disease who are pregnant and planning to become pregnant.

Keywords

Crohn's disease, Pregnancy, Incidence, Risk, Treatment

1. Introduction

As a chronic inflammatory disease of the digestive system, the cause of Crohn's disease is unclear. There are various theories to discuss the cause of this disease, such as intestinal infection factors, immune mechanism, food, chemical substances, injury, insufficient blood supply, and mental and psychological factors, etc. In recent years, with the changes in environment and lifestyle, the incidence of Crohn's disease in different countries has increased significantly. The study by Zheng et al. [1] point out that the number of Crohn's disease patients (2,149 cases) in China during the five years (from 2003 to 2007) is 1.41 times of the 1,526 cases in the past 50 years. The estimated average incidence of Crohn's disease is 12.21 per 100,000 person-years. Although the incidence of Crohn's disease in China is lower than in developed countries, pregnancy is a dangerous period and various complications are prone to occur. Therefore, under the same conditions, the probability and risk of Crohn's disease during pregnancy are

higher than that of men and non-pregnancy. Deng et al. propose that childbirth and cesarean section are a cause of Crohn's disease [2]. Cornish et al. proposed that Crohn's disease occurs in people aged 20 to 30, and the incidence of women in high-incidence areas is slightly higher than that of men [3]. Women's onset of Crohn's disease is about 20% to 30% higher than men's, and it would be exacerbated during pregnancy and childbirth [4]. Therefore, it is clear that the incidence of Crohn's disease during pregnancy is higher than that of men and adults during non-pregnancy.

Since pregnancy is a critical period for women as well as their baby and Crohn's disease is more likely to occur during this time, we need to study the incidence, risk and treatment of Crohn's disease during pregnancy. In this paper, we summarize and generalize the advances in research of the incidence, risk and treatment of Crohn's disease during pregnancy. Section 2 describes the risk caused by Crohn's disease during pregnancy. Section 3 analyzes the researches on the treatment of Crohn's disease during pregnancy.

2. Incidence and Risk of Crohn's Disease during Pregnancy

The influence of Crohn's disease on pregnancy mainly depends on whether the disease state of Crohn's disease during pregnancy and childbirth is active or quiescent. And the disease state is determined by the characteristics of the disease itself, the clinical course and the drug responsiveness of treatment [5]. A recent meta-analysis shows that the risk of Crohn's disease during pregnancy is higher than the risk of pregnancy during active disease [6]. Khosla et al. consider that when pregnant with Crohn's disease in the active period, about 1/3 of the patient's condition will be relieved, 1/3 pregnant women's Crohn's disease will be persistent, another 1/3 pregnant women's Crohn's disease will be worsening [7].

Common complications of Crohn's disease during pregnancy include miscarriage, anemia, malnutrition, perianal inflammation, perianal abscess, emotional depression, etc. Abdominal pain and diarrhea caused by Crohn's disease will increase intestinal peristalsis, which would stimulate the nearby uterus, result in uterine contraction, and lead to miscarriage or premature delivery. Cornish et al. [8] point out in a meta-analysis that if the disease occurs during pregnancy or outbreaks, it can significantly increase the incidence of miscarriage, stillbirth, premature delivery, low birth weight and birth defects. However, some scholars believe that Crohn's disease will be relieved during pregnancy, but often recurring during early pregnancy [9].

The blood picture of Crohn's disease is as follows: decreased hemoglobin, increased erythrocyte sedimentation rate, decreased albumin, and increased white blood cells. The red blood cell count during pregnancy drops to 3.6*1012/L (normal 4.2*1012/L), which is prone to physiological anemia; hemoglobin value drops to 110g/L (normal 130g/L); white blood cells will increase, and immune function would be strengthened; total plasma protein decreased by 60g/L (normal 70g/L), mainly because albumin decreased from 40g/L to 25g/L, and some nutrients in plasma decreased (glucose, amino acids, iron, water-soluble vitamins). Therefore, when Crohn's disease occurs in pregnant women, the patient's hemoglobin, albumin and red blood cell counts are significantly reduced, so anemia and malnutrition are prone to occur. Coupled with the increase in nutrients required by pregnant women during pregnancy, malnutrition is prone to occur. At the same time, chronic diarrhea is also an important cause of malnutrition.

During pregnancy, due to the growth of the fetus, the uterus gradually enlarges, and the pressure on the blood vessels in the pelvis is also increased, which affects the venous return of the anus and rectum. This would lead to congestion and dilation of hemorrhoidal veins. Moreover, pregnant women with Crohn's disease will get long-term diarrhea, which would induce and aggravate hemorrhoids condition. Prolapsed internal hemorrhoids, external hemorrhoids, and mixed hemorrhoids can affect the cleansing of the stool, which leads to residual stool in the anus. In addition, the resistance of pregnant women is reduced. Therefore, perianal inflammation and perianal abscess are prone to occur. This may be one of the reasons that lead to high recurrence rate of Crohn's disease during pregnancy.

In addition, patients who get Crohn's disease during pregnancy are prone to having psychological disorders. Studies have found that long-term depression of patients seems to be one of the risk factors for disease recurrence, which seriously threaten the life safety of pregnant women and baby [10]. The common clinical type of mental disorder is depression. Its typical manifestations are "three lows", namely depression, loss of interest, and lack of energy. At the same time, it can be accompanied by anxiety, insomnia, and loss of appetite. In severe cases, even suicide or infant injury tends to occur.

According to statistics [11], the pre-pregnancy disease is in a quiescent period. The recurrence rate of the disease during pregnancy is 9%-39%, and most of the recurrence occurs in the first 3 months of pregnancy and the puerpe-

rium. The repetition of the disease will significantly increase the incidence of the above complications and the degree of damage. The risk of complicated Crohn's disease during pregnancy is high. But in clinical diagnosis, pregnant women are not suitable for many examinations, thus the diagnosis becomes more difficult. In such circumstances, joint diagnosis and treatment of obstetrics and gynecology as well as gastroenterology is required.

3. Treatment of Crohn's Disease during Pregnancy

The most concerned problem of researchers is the effective treatment of Crohn's disease. However, despite researchers putting in a lot of effort, there is no way to cure Crohn's disease. Crohn's disease currently lacks effective approaches to cure. Clinical treatment usually uses drug treatment to control disease activities and maintain disease relief, prevent complications, and prevent intestinal damage [12].

To date, Crohn's disease has not been completely cured. Drugs for Crohn's disease include traditional drugs (sulfasalazine, mesalazine), Adrenal cortex hormones (immunosuppressive), Immunosuppressive agents (azathioprine), Biological agents, TNF α antibodies (infliximab), Vedolizumab (anti-α4β7), Etrolizumab(anti-β7 antibody), PF-00547, 659(anti-MACLCAM-1 antibody), and Tofacitinib (inhibition of Janus kinase 1, 2 and 3) [13]. Ineffective drug treatments or those who have severe complications such as complete intestinal obstruction, acute perforation, uncontrollable hemorrhage, etc., may consider surgical treatment [14].

Except for drug treatment, treatment through surgery is also an important way to deal with Crohn's disease. Surgical treatment is required for 80% of Crohn's disease, but surgery is not a radical measure. Common surgical treatments for Crohn's disease include diseased bowel resection. Patients with fistula and abdominal abscesses are recommended to undergo ultrasound or CT-guided abscess puncture and drainage. Laparoscopic surgery is recommended for intestinal fistula complicated by Crohn's disease with mild adhesions [16-17]. However, surgical treatment usually has high recurrence rate, and most patients need medication to prevent recurrence. According to statistics [18], if no treatment is given after Crohn's disease operation in the ileocecal area, the recurrence rate under endoscopy within 1 year is 65% to 90%, and it can reach 80% to 100% in 3 years. There are many contraindications to medication during pregnancy, so it is recommended that maintenance therapy should be actively carried out during the inactive period of pregnancy. The course of maintenance treatment for Crohn's disease is still unclear. Mercaptopurine drugs are used for long-term maintenance after remission induced by hormones. Patients can continue to use it for maintenance therapy or switch to immunosuppressive agents for maintenance after the application of biologics to treat remission. The initial recommendation for the course of treatment of biological agents is to continue to consolidate the medication for 1 year after the intestinal ulcer is found to be completely healed by the endoscope. And then, the medication can be considered to be discontinued, but it is still recommended to continue with mercaptopurine drugs [19].

In clinical practice, symptomatic treatment can be given for complications, such as malnutrition, enteral nutrition preparation, etc. can be used in the care of a case of Crohn's disease during pregnancy. In this way, intact protein enteral nutrition powder is the only source of nutrition, which can completely replace the diet [20] and would get a better curative effect. Huang et al. believe that enteral nutrition supportive care has a better therapeutic effect on the remission period of Crohn's disease than other treatment methods, with a higher remission rate and sustained remission rate, and fewer adverse reactions [21].

There is no significant difference between the medication used in the active phase and non-pregnant patients. However, when choosing a drug, the risk or benefit ratio of the drug should be carefully considered. According to the European Expert Consensus of Crohn's disease in 2010 and related literature [22-24], drugs that can be used safely during pregnancy are 5-ASA, SASP, Glucocorticoids, Antibiotics, and Anti-TNF-α monoclonal antibodies. Budesonide, Thiopurines, Tuinolones, CsA, FK506, etc. are relatively safe drugs. However, MTX, Sulfonamides, Tetracycline, Thalidomide, etc. have obvious teratogenic effects on the fetus, and use of them should be prohibited. It should be noted that although the FDA classifies AZA and 6-MP in category D, there is evidence that there are risks to humans, and the risk or benefit ratio should be carefully considered [25]. Francella et al. [26] treated 341 patients with inflammatory bowel disease (IBD) who used AZA or 6-MP during pregnancy. All of them gave birth normally, and the incidence of premature delivery, spontaneous abortion, congenital abnormalities, or neonatal infections did not increase. Therefore, it is considered safe to use such drugs during pregnancy. Dejaco et al. [27] also confirmed that the prognosis of thiopurine-treated Crohn's disease patients during pregnancy is consistent with that of non-users. Therefore, comprehensive consideration is needed when choosing drug treatment to reduce meaningless administration.

For severe diarrhea during the active period, alternative treatment can be combined with bifid triple viable bacte-

ria tablets and montmorillonite powder. Li et al. [28] found that the alternate application of the two drugs can have a synergistic effect, which not only avoids the adverse effects of antibiotics or other drugs on pregnant women and fetuses as well as the related flora imbalance and microecological imbalance, but also can play a role of rapid anti-diarrheal.

There is still controversy about the best delivery method for Crohn's disease during pregnancy. At present, it is clinically more inclined to choose cesarean section to terminate pregnancy [29]. The latest research suggests that pregnant women with active perianal Crohn's disease have more complications, and vaginal delivery should be avoided [30]. For inactive Crohn's disease, if there is no perianal disease, a trial vaginal delivery can be considered. If there is dystocia or fetal distress, a cesarean section should be performed immediately without observation. Some scholars have suggested that for ulcerative colitis (UC) patients or Crohn's disease patients with the active perianal disease after IPAA, cesarean section is recommended [31]. According to current clinical observations and recommendations, if no medication or use drugs such as glucocorticoids, 5-ASA, thiopurine drugs, and infliximab, breastfeeding will not be affected. Therefore, patients can rest assured to choose breastfeeding. Breastfeeding can not only prevent the recurrence of inflammatory bowel disease (IBD) but also protect or delay the time of inflammatory bowel disease (IBD) for offspring [32-33].

During treatment and follow-up, clinicians need to pay attention to the patient's mental state and health-related quality of life. If the patient has a mental health disorder, the patient should be advised to receive psychological treatment. Once the patient has psychological obstacles, it is necessary to find active treatment and provide professional psychotherapy according to the type of patient mental disorder. If the mother wants to kill the baby, the medical staff needs to observe the mother closely and separate the mother and the baby. It is necessary to use psychotropic drugs [34]. The concern of family is also extremely important. The psychological barriers of most pregnant women are related to the ignorance and indifference of family members. In addition to blindly strengthening nutrition, family members should also communicate with pregnant women more frequently. Family members should understand and sympathize with the pain of pregnant women, and give care. Patients with a history of psychiatric genetic disease and previous psychiatric history should be closely observed. If abnormalities are found, relevant treatment should be carried out immediately. Studies have found that psychotherapy has a positive effect on the activity of Crohn's disease and ulcerative colitis (UC). Therefore, attention should be paid to the mental health of pregnant women.

4. Conclusion

Crohn's disease during pregnancy is a very dangerous disease that seriously threatens the lives of pregnant women and fetuses. Due to the lack of a radical cure for Crohn's disease, it is necessary to pay great attention to the condition of pregnant women, choose symptomatic medical treatment or surgical treatment, and plan for maintenance treatment. In addition, Crohn's disease during pregnancy is prone to psychological disorders. During treatment and follow-up, clinicians need to pay attention to the patient's mental state and health-related quality of life. If the patient has a mental health disorder, the patient should be advised to receive psychological treatment. Pregnant women with Crohn's disease in the quiescent period are similar to ordinary pregnant women in terms of spontaneous abortion, pregnancy complications and adverse pregnancy outcomes [35]. Therefore, women of childbearing age should try to avoid pregnancy during Crohn's disease active period, such as if an acute attack of Crohn's disease occurs during pregnancy, conservative treatment should be actively carried out. If it fails, labor should be induced immediately to protect the mother. When Crohn's disease occurs during pregnancy, stay calm, master the principles of treatment and medication, and turn the active period of Crohn's disease into remission as much as possible to achieve a better prognosis. The pathogenesis of Crohn's disease and effective drugs is still a difficult problem, and it is also a research direction in the future.

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