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Safety of Biologic Therapy in Pregnant Patients with Inflammatory Bowel Disease.

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Abstract

Background*: Inflammatory bowel disease (IBD) is a chronic disease with major impact on pregnancy as it affects young people in their productive years. Biological management could be used as induction therapy or maintenance of remission for IBD patients. However, the effect of biological agents on the long run for the offspring is still unclear. Moreover, Their benefits might outweigh the flare complications which includes preterm birth, lower birth weight, small for gestational age, spontaneous abortion, stillbirth, and infections with no increase in congenital anomalies for IBD pregnant women. Therefore, it is essential to assess the influence of biological agents' exposure before and during pregnancy regarding pregnancy consequences. Most pregnant IBD patients with remission will have normal pregnancy.*

Objective: *This study aims to evaluate and help guide physician in regrade to the safety of biological agents with IBD pregnant women and their effects on pregnancy outcome*

Conclusion:

There was no significant association between the biological management of IBD during pregnancy, even until the third trimester, and poor pregnancy outcomes. This is Including preterm birth, lower birth weight, small for gestational age, spontaneous abortion, stillbirth and infections with no increase in congenital anomalies. The benefits of continuing the biological agents in IBD pregnant patients might exceed the adverse pregnancy outcomes resulting from flares [(7)]. However, biologics could be discontinued at the end of the second trimester if the pregnant women had sustained remission by using the stopping criteria for patients with IBD. Conversely, because of the highly negative outcomes in discontinuing the biologic agent in active disease on the mothers and their children, maintaining medical treatment is probably the best option. Also, as a study showed, pregnancy might have a favorable influence on IBD patients leading to postpartum reduction of relapse in both CD and UC. Preconception counseling with gastroenterologist and obstetrician with IBD patients determining to get pregnant is urged. The counseling should focus on the medical treatment and its consequences and the effects of IBD disease activity on pregnancy. Ideally, conception should occur in remission periods.

Keywords*: Inflammatory bowel disease, Crohn's disease, Ulcerative colitis, Biologic, Anti-tumor necrosis factor Alfa.*

Introduction

Inflammatory bowel diseases] (IBD) is a chronic autoimmune disease with multifactorial etiologies; most likely owing to a sustained response to the immune system after an infection in a genetically predisposed individual. It consists of two disorders: Crohn's Disease (CD) and Ulcerative Colitis (UC). These two disorders might have some common characteristics and overlaps but they are to some extent differ in their clinical and pathological manifestations. (6,7,8)

CD affects the trans-mural intestinal layers with skip lesions of any part of the gastrointestinal system, from the mouth to the peri-anal region, and mostly located in ileum and proximal colon. Endoscopically, it has linear ulcers leading to mucosal island and cobblestone appearance. Whereas, UC affects mainly the mucosal layers and present in the large bowel. The rectum is always involved in UC, and the lesions extend proximally until it reaches the cecum with continuous diffuse inflammation. (8)

Histological differences (granuloma)

The prevalence of IBD has increased from 3.7 million to 6.8 million in 1990 to 2017, respectively. (9,10) There is no significant difference about IBD incidence between both sex, however, there has been slight increase in incidence with female adult-onset Crohn's disease. (8)

This led to our main Focus, which is the onset of the disease in females' childbearing ages and its impact on pregnancy. Additionally, the effects of the disease's behaviour and influence of its medication on both mother and fetus during pregnancy and postpartum period. (8,10)

Medication non-adherence during pregnancy is an important factor to look at. In one study included 143 491 IBD women who were previously adherent to medical therapy showed a quarter of them become non adherents to their medication during pregnancy because of misunderstanding and poor perspective toward medication and the vague influence on the long run result toward their children. (3) Patients attending to get pregnant have concerns regarding the ability to become pregnant, coping with the disease in preconception, peripartum and postpartum and the medication safety as regard to these periods on their offspring's. (9,15)

This disease with its relapses and remissions course needs lifelong intensive medical management to maintain its quittance even with pregnancy. (1) For that We aim in this paper to focus specifically on the biological medication safety in pregnancy outcomes.

Effect of IBD on Fertility and Pregnancy

There is no difference in fertility from IBD female patient in remission with no previous surgical intervention in compare with the general population.

Nevertheless, females with active disease might have lower fertility rates. (6,12) A Danish study revealed 4 reasons behind the delay of conceiving in CD patients. First, decrease libido in IBD patient which has been coupled with depression disease, bowel surgeries, IBD activity and other medication such as psychoactive drugs. Second, females over the age of thirty with CD have decreased ovarian reserve which is considered to be due to the disease's activity. Third, disease activity has been linked to lower the fertility in a single study (Source). Lastly, surgeries specifically ileal pouch anal anastomosis (IPAA) causing scarring or inflammation to the fallopian tubes or as in perianal disease which can cause dyspareunia (15). Women who suffer from these problems may need preconception counseling to correct any misunderstanding or misconception issues. This include healthier behavior choices, improvers the pregnancy outcomes optimized disease management by increase the adherence of the medication, reduce the relapse and flare, smoking cessation and optimized the nutritional statues (optimizing folate, iron and vitamin 12 consummations). (7)

Transmission of the disease to their children. As in first degree relative, the increase of transmission is closely 3-20 times more in compare to the general populations. As mentioned by a cohort study, the genetic risk of having a child with CD and UC regarding maternal setting is about 7.7% for IBD mothers and 4.6% for free IBD ones (9). The percentage can increase up to 30% when both of the parents are affected.

Who are considering pregnancy should be in a remission period of the disease. The remission period estimated to be three to six months on stable medication before, during pregnancy and until twenty weeks of gestation. (1,7) In general, pregnant women with quite IBD have a good uncomplicated pregnancy and postpartum outcomes.

In CD, disease courses are nearly the same as non-pregnant IBD women. However, around one third of the patients who get pregnant with quiet disease have risk of relapse. (12)

The exacerbations of the disease activity frequently exhibited in the first trimester of pregnancy owing to the cessation of maintenance medication. Further, patients who have reached remission in pregnancy probably will hold their medications the rest of the pregnancy. (14)

Active disease during pregnancy has been associated with preterm birth, lower birth weight, small for gestational age, spontaneous abortion, stillbirth and infections with no increase in congenital anomalies. (7)

Moreover, there were other adverse events affecting the mothers such as active perianal Crohn's, surgical interventions during pregnancy and venous thromboembolism with pulmonary embolism being the main cause of deaths predominately in hospitalized patients with flare. Roughly 70 % who have an active disease at conception will carry it on or have an active disease during pregnancy. (7,9)

Effect of pregnancy on IBD

A retrospective study estimated that there is a reduction in the disease activity during pregnancy, although the reduction was partially because of the cessation of smoking in that period. (12) Additionally, lower levels of pro-inflammatory markers (interleukin (IL) IL6, IL8, IL12, IL17 and TNFα) on conception and changes in the intestinal microbiome throughout middle to late pregnancy were observed. As a result, it was suggested that pregnancy has a favorable outcome on IBD patients. (13) Regarding flare, a cohort study showed similarity in CD flare rates 14-34% during pregnancy for IBD pregnant patients, who conceive in remission, and IBD non-pregnant patients. While 2\3 showed an increase in flare when conception occurred in an active disease. In addition, complications of pregnancy such as preterm delivery are linked with flares during pregnancy. The higher risk of relapse has been seen in UC rather than CD. CD has no high risk of flare nor disease course, it is just about the same to non-pregnant patients. (9,12) On the subject of congenital malformation risks, according to a retrospective cohort study done in 1997 the risks were 7.9%, 3.4% and 1.7% in UC, CD and controls, respectively. This report shows a slight increase in risk of congenital anomalies, especially in UC active disease. (14)

Moreover, getting pregnant when the disease in remission exhibits an increase in quality of life and reduces the flare risk nearly to ten years postpartum in both disorders. On the other hand, having an active disease in conception could have a higher risk of disease activity and flare during pregnancy and\or postpartum. (12)

Biological IBD management

The management of IBD pregnant patients should be individualized case by case bases with a multidisciplinary team approach.

Biologics are effective choice to use in initiation of remission or as maintenance therapy for IBD. However, it's effect in short-term and long-term in both the mother and fetus it's still unclear. So far, the use of the biological agents is based on the physician's expert opinions. (6)

Antitumor necrosis factor (anti TNF) including infliximab, adalimumab, vedolizumab and ustekinumab are all IgG1 monoclonal antibodies. Whereas Certolizumab pegol does not have a Fc portion, thus it can't be transported via the placenta and considered to be safe throughout pregnancy. (6,12) All are classified as category B meaning the trials failed to show teratogenicity effects of this medication on animals. Additionally, Nataliumab which is IgG4 α classified as category C meaning this medication might causes a negative or harmful effects on the fetus with no congenital malformation. (4,6)

IgG antibodies are actively transported from the placenta to the fetus by the use of an active mechanism consisting of pH dependent binding of immunoglobulins by the Fc portion of the fetus starting at week 20-22. (14) The use of these medications in the third trimester results in high exposure to the fetus, this is why they are usually stopped from 20-24 weeks or within the third trimester. The clearance takes approximately 6 months. Although, infliximab has been reported to stay in the infant blood level up to 1 year for mothers who took it until delivery. The immature reticuloendothelial system has a slow rate of clearing the antibodies which might be the cause of this consequence. (6,12)

The literature has demonstrated that biological agents had no negative effects on female fertility. It suggested that biologics have a favorable effect on fertility due to the reduction of surgeries and its complications. (6)

Infliximab

Infliximab is the commonest biological medication used in IBD pregnant patients. (7) As determined by the therapy resource evaluation assessment tool (TREAT), which is a prospective study for CD, there was no increase of reported malformation cases in exposed mothers with IBD compared with the non-IBD population. Moreover, the rate of natural abortion was 11.1% vs. 7.1 % and neonatal complications were 8.3 vs. 7.1% in comparison to exposes IBD mother and non-exposed mother. Even though, it could be associated with the disease activity as only lower percentage of the pregnant women were in remission. (14,15)

It could take up to one year for infliximab to be cleared for the children's systems if the mothers continued it until the third trimester. Therefore, concerns have been raised about its effects on the long run to the offspring's immunity systems. Additionally, exposure of infliximab in an intrauterine environment until 30 weeks of gestation, will result in increased infliximab blood level of the neonate up to 4 fold more than the mothers. (7) Consequently, the use of live attenuated vaccines (like measles, mumps, rubella; MMR, Bacillus Calmeete-Gue'rin; BCG, Rotavirus ...etc.) is contraindicated. For instance, a case report stated a fatal incidence of disseminated Tuberculosis infection for a 3 months child who took BCG vaccine. The child was born to an infliximab exposed mother during gestation. For that reason, World Congress of Gastroenterology recommended to delay all live-virus vaccines to all infants exposed to biologic therapy in utero until they are having free blood level of biologics. (6)

According a systematic review done at 2013, the prevalence of complicated pregnancy outcomes (low birth weight, miscarriages, preterm delivery, congenital anomalies or stillbirth) for infliximab exposed women during pregnancy even in the third trimester was limited. (6)

Adalimumab

There was no increased risk of negative pregnancy outcomes or congenital anomalies for children exposed to adalimumab in intrauterine period. Even if it was given until the third trimester for mothers with IBD (reference). In comparison to the general population or IBD pregnant women who did not receive adalimumab with exposed IBD pregnant women, there was no difference in adverse pregnancy outcomes (preterm delivery, miscarries, congenital anomalies and stillbirth). Furthermore, pregnancy in inflammatory Bowel Disease and Neonatal Outcomes PIANO, a study with 1232 pregnant women, revealed no increase of congenital anomalies nor infections to children exposed to biologics medications (reference). On the other hand, Organization of Teratology Information Specialist OTIS, a prospective study done from 1999-2009, included only Adalimumab and etanercept showed 7-10% of offspring had congenital abnormalities. Even though the disease activity could be a confounder that caused elevation of these effects. (6.7)

Certolizumab pegol

Certolizumab pegol lacks the Fc portion therefore it has a limited placental transportation with its Fab portion. Moreover, there is inadequate literature regarding this medication. However, certolizumab pegol is considered to be on the lower risk side, that's why it is theoretically safe to be used before, during and after pregnancy. (14)

Natalizumab

This medication is an α4 integrin inhibitor (a humanized IgG4 isotype antibody) actively transported via the placenta with lower efficiency compared to IgG1 medication used in the United States. It is commonly used for multiple sclerosis (MS), it has limited data for its utility on IBD. As demonstrated by a study with 164 pregnant women, administration of natalizumab in the first trimester had no unfavorable outcomes. (15)

Ustekinumab

In literature, there is insubstantial data in respect of ustekinumab use in IBD pregnant patients. A study with 206 pregnancies using ustekinumab with only 36 patients who had CD, reveled no difference in the rate of abortions or congenital malformation with general populations. (15)

Vedolizumab

Discussion

There was no support for the discontinuation practice of biological medication to IBD mothers after 30 weeks of gestation. As theoretically, there was no increased risk of infection, congenital anomalies or poor pregnancy consequence in comparison with the general population. Nevertheless, the children of these women should not receive live vaccines until the biological medications are cleared from their system due to the risk of lethal infections. (6) Therefore, pediatricians should be notified in these cases concerning this subject. (14) The safety of biologics results is reassuring on the subject of using them during conceiving and pregnancy. (15) However, biologics should be stopped throughout pregnancy if the IBD patients reached a sustained remission by using the stopping criteria for patients with IBD in general. On the report of a prospective study with 29 pregnancies, the stopping of biological agents in the second trimesters could result in significant lowering of the anti-TNF agents in the newborn's cord blood level with no raise of the risk of relapses. Another prospective cohort study done in 2015 with Almost 6 years follow up consist of over 100 pregnant IBD patient using anti-TNF until 20-25 weeks of gestation reported, discontinuing the biological agents does not result in increasing the risk of relapses in pregnant patients with sustained remission in compare with the women with IBD who did not stop the medications. It was also mentioned no increase in allergic reactions or loss of response to anti-TNF if reinitiated after delivery. (1) Additionally, the continuation of the biologics should be considered in active disease at the end of the second trimester as the benefit of anti-TNF outweighs the risk. Although, there is a concern relating to the long-term influence of the anti-TNF consumptions beyond the second trimester as to the development of offspring's immune system. (11) A study with almost 2 years follow-up post-delivery showed similarity in the incidences of severe infections between intrauterine biologics exposed and non-exposed children. In addition, there was no difference reported in psychomotor development or growth in the exposed children in compare with non-exposed ones. Nevertheless, higher ICU admissions and prevalence of low birth weight were outlined in the exposed group. (15)

Pregnant women with an active disease who stopped anti-TNF before 24 weeks of gestation, had a higher chance of developing relapse compared to the ones who continued the medications in the time of active disease. (12) Nonetheless, according to EVASION, a retrospective cohort study, continuing the anti-TNF through pregnancy in IBD patients is related to complications to mothers, specifically infections, in comparison with non-exposed pregnant patients. However, the study supported the maintenance of anti-TNF for active disease, because the active disease course has more unfavorable outcomes to the pregnancy. Additionally, the study suggested no significant increase in complications (particularly severe infections) to the mothers who were treated with anti-TNF during the third trimester and the ones who ceased the medications. It also stated a slight increase in premature birth with no significant negative events to exposed children. (5)

In addition, there is no increase in growth, infections, hospitalized admissions, allergies and eczema to exposed children to anti-TNF in compare to the non-exposed children. Studies continually showed no

increase with negative outcomes neither to the mothers nor newborns. (1) other biologic agent was not included the discussion

Conclusion

There was no significant association between the biological management of IBD during pregnancy, even until the third trimester, and poor pregnancy outcomes. The benefits of continuing the biological agents in IBD pregnant patients might exceed the adverse pregnancy outcomes resulting from flares.(7) However, biologics could be discontinued at the end of the second trimester if the pregnant women had sustained remission by using the stopping criteria for patients with IBD. Conversely, because of the great negative outcomes in discontinuing the biologic agent in active disease on the mothers and their children, maintaining medical treatment is probably the best option. Preconception counseling with gastroenterologist and obstetrician with IBD patients determining to get pregnant is urged.

References

1. de Lima A, Zelinkova Z, van der Ent C, Steegers E, van der Woude C. Tailored anti-TNF therapy during pregnancy in patients with IBD: maternal and fetal safety. Gut. 2015; 65(8):1261-1268.

2. Friedman S. Pregnancy and IBD: Timing Is Everything. Digestive Diseases and Sciences. 2017; 62(8):1847-1849.

3. Lee S, Seow C, Adhikari K, Metcalfe A. Pregnant women with IBD are more likely to be adherent to biologic therapies than other medications. Alimentary Pharmacology & Therapeutics. 2019; 51(5):544-552.

4. Leung H, Saini B, Ritchie H. Medications and pregnancy: The role of community pharmacists – A descriptive study. PLOS ONE. 2018; 13(5):e0195101.

5. Luu M, Benzenine E, Doret M, Michiels C, Barkun A, Degand T et al. Continuous Anti-TNFα Use Throughout Pregnancy: Possible Complications For the Mother But Not for the Fetus. A Retrospective Cohort on the French National Health Insurance Database (EVASION). American Journal of Gastroenterology. 2018; 113(11):1669-1677.

6. Nielsen O, Loftus E, Jess T. Safety of TNF-α inhibitors during IBD pregnancy: a systematic review. BMC Medicine. 2013; 11(1).

7. Nielsen O, Maxwell C, Hendel J. IBD medications during pregnancy and lactation. Nature Reviews Gastroenterology & Hepatology. 2013; 11(2):116-127.

8. Peppercorn M, Cheifetz A. Tools Definitions, epidemiology, and risk factors for inflammatory bowel disease [Internet]. Uptodate.com. 2021 [cited 26 December 2021]. Available from: https://www.uptodate.com/contents/definitions-epidemiology-and-risk-factors-for-inflammatory-bowel-disease#!

9. Peppercorn M, Mahadevan U. Fertility, pregnancy, and nursing in inflammatory bowel disease [Internet]. Uptodate.com. 2021 [cited 20 December 2021]. Available from: https://www.uptodate.com/contents/fertility-pregnancy-and-nursing-in-inflammatory-bowel-disease#!

10. Ray K. The changing epidemiology of IBD. Nature Reviews Gastroenterology & Hepatology. 2017; 14(12):690-690.

11. Schulze H, Esters P, Dignass A. Editorial: the management of IBD during pregnancy and lactation - author's reply. Alimentary Pharmacology & Therapeutics. 2014; 40(10):1248-1248.

12. Selinger C, Nelson-Piercy C, Fraser A, Hall V, Limdi J, Smith L et al. IBD in pregnancy: recent advances, practical management. Frontline Gastroenterology. 2020; 12(3):214-224.

13. van der Giessen J, Binyamin D, Belogolovski A, Frishman S, Tenenbaum-Gavish K, Hadar E et al. Modulation of cytokine patterns and microbiome during pregnancy in IBD. Gut. 2019; 69(3):473-486.

14. Vermeire S, Carbonnel F, Coulie P, Geenen V, Hazes J, Masson P et al. Management of inflammatory bowel disease in pregnancy. Journal of Crohn's and Colitis. 2012; 6(8).

15. Winter R, Friedman S. Update on Pregnancy in Patients with IBD. Current Treatment Options in Gastroenterology. 2020; 18(3):423-441.