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Safety of IBD Medication During Pregnancy and Conception for Men and Women with Inflammatory Bowel Disease

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Inflammatory bowel disease (IBD) has an increasing prevalence worldwide, including young adults. Fertility and pregnancy safety are common topics of concern in this patient population. Maintaining fertility and achieving healthy maternal and fetal outcomes are dependent on disease severity. Steroid free remission for at least three months prior to conception increases the likelihood of sustained remission throughout pregnancy and decreases the risk of pregnancy related complications for both the mother and child. Data from large registries, including PIANO (Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes), has demonstrated that biologics and thiopurines are low risk during pre-conception, pregnancy, delivery, and lactation. Children with in utero or breastmilk exposure to these medications are not at increased risk of infection during their first year of life and achieve developmental milestones at a rate consistent with that of the general population. Methotrexate must be avoided due to the risk of teratogenicity. Data to support use of small molecule therapies during pregnancy and breastfeeding is lacking at this time.

INTRODUCTION

Inflammatory bowel disease (IBD) is commonly diagnosed between the ages of 18 and 35 years old, a period when many patients are considering having children of their own.[1] The prevalence of IBD is continuing to rise, and there are approximately 3.1 million people in the U.S. who carry a diagnosis of IBD today. This number is anticipated to go up further. The increasing prevalence of IBD in young adults makes conception and pregnancy in IBD a topic of high importance for gastroenterology providers.[2]

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Fertility

Infertility is defined as the inability to conceive after 12 months of regular, unprotected sexual intercourse.[3] In the IBD population, however, a referral to a fertility specialist is suggested after 6 months.[4] There are multiple factors that play a

role in fertility including psychological factors, history of bowel surgery, zinc deficiency, certain medications, and alcohol and tobacco use.

IBD medications that may contribute to male infertility include methotrexate and sulfasalazine.[5] 5-aminosalicyclic acid (5-ASA) typically does not impact fertility,[6] but sulfasalazine is associated with reversible oligospermia and should be discontinued three to four months prior to attempted conception.[7,8]

Methotrexate can also result in oligospermia which is reversible with discontinuation of the drug. Biologics and thiopurines do not have any documented impact on fertility.[9,10] Data on the fertility risk of approved small molecule drugs, tofacitinib and ozanimod, are lacking at this time.[11,12]

Other medications used to manage conditions associated with IBD must also be considered. Anxiety and depression have a high prevalence in the IBD population, and the use of psychotropic drugs is common.[13] Selective serotonin reuptake inhibitors can cause ejaculatory dysfunction, increased ejaculation latency, and alteration in circulating hormones.[14,15] Furthermore, opioid analgesics significantly increase the risk of erectile dysfunction.[16,17,18] Zinc deficiency may also be a contributing factor to infertility and levels should be checked when this is a concern.[19]

Fertility in women is not impacted by most IBD medications. However, methotrexate should be discontinued in women three months prior to conception due to the risk of teratogenicity.

Most surgical management for IBD does not impact fertility in men or women, including limited bowel resection or surgical management of perianal disease. However, total colectomy with ileal pouch anal anastomosis is associated with a 3-fold higher rate of infertility among women and attributed to fallopian tube scarring from pelvic dissection.[20,21,22]

Pre-Conception

Disease Activity

Patients should achieve at least three months of steroid free remission, both clinical and endoscopic, prior to conception. The importance of remission should be emphasized with all women of child-bearing age to ensure that they are in optimal health for conception if and when the time comes.[4,23] Women with IBD who conceive while in remission will remain in remission 80% of the time whereas those with active disease will either continue to have active or worsening disease in over 60% of cases.[24,25] Active disease during pregnancy portends a poor outcome for the mother and fetus and will increase the likelihood of eclampsia, preterm birth, low birth weight, small for gestational age, and poor maternal weight gain leading to intrauterine growth restriction.[26-28] On the other hand, pregnancy outcomes in IBD patients with quiescent disease are similar to the general population.[29,30]

IBD Heritability

Misconceptions regarding heritability have led to voluntary childlessness among men and women with IBD. While genetic inheritance plays a strong role in IBD, other modifiable factors influence heritability including environmental exposures such as tobacco smoke, diet, and air pollution.[31] It is suspected that the interaction of genetics under environmental conditions is what leads to the increased incidence of IBD among family members.[32]

Healthcare Maintenance

Optimizing maternal health prior to conception is critical. Alcohol, tobacco, recreational drugs, and cannabis should all be discontinued. Continued opioid use during pregnancy can lead to neonatal opioid withdrawal syndrome and long-term neurodevelopmental consequences.[33,34] Furthermore, women should aim for a healthy body mass index (BMI); increased pre-pregnancy BMI can lead to gestational diabetes, hypertensive disorder, and Caesarean delivery.[35]

All patients should be up to date with age-appropriate cancer screening including colon cancer screening in those with more than 8 years of colitis, regular pap smears in women, and annual total body skin exams for all patients on thiopurines and biologic therapies.[36]

Nutrition

Women planning pregnancy should supplement with folic acid 400 micrograms (μg) daily. A minimum of 2 grams of folate daily is suggested for those with a prior small bowel resection or active small bowel disease. Vitamin D

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supplementation is recommended for all patients, and its administration may decrease the risk of flares in those with ulcerative colitis.[37] Vitamin D, zinc, folate, vitamin B12 and other nutritional markers should be evaluated pre-pregnancy and thereafter as needed.[4,38-40]

Pregnancy

Coordinated Care

Coordinated care among multiple specialties and teams is needed to ensure good maternal and fetal outcomes.[41,42] A gastroenterologist, ideally one who specializes in IBD, should follow the patient throughout pregnancy, seeing the patient at least once during the first or second trimester and as needed thereafter.[4] A maternal fetal medicine specialist should be involved early in pregnancy, regardless of disease activity. A nutritionist, mental health provider, and lactation specialist knowledgeable about IBD drugs may be of assistance as well.[4]

Disease Flare

Disease activity can increase during pregnancy leading to adverse outcomes. Controlling disease activity prior to conception and during pregnancy with the appropriate medical therapy can mitigate the risk of spontaneous abortion, preterm birth, and labor complications (Figure 1).[43]

As in non-pregnant IBD patients, when disease activity flares, infection must be ruled out first with evaluation of stool studies. In pregnancy, diagnostic evaluation to obtain objective evidence of inflammation with non-invasive markers is preferred. Inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may not be as reliable in the pregnant patient, although monitoring overall trends can be helpful.[44] Fecal calprotectin (FCP) does rise in correlation with disease activity as well.[45,46] Imaging studies can be pursued to obtain further objective information, and MRI without gadolinium or intestinal ultrasound (where available) is preferred.

A flexible sigmoidoscopy can be safely performed during any trimester without sedation and limited preparation with enemas and is preferred over pan-colonoscopy.[47] However, when necessary, a complete colonoscopy can be performed in the pregnant patient as well.[48] The American Society for Gastrointestinal Endoscopy (ASGE) guidelines suggest placing the patient in the left lateral tilt position to avoid decreased maternal and placental perfusion.[49]

Treating a disease flare may consist of using a short course of steroids, increasing medication dose, and changing therapy. When medical therapies prove ineffective, surgery can be pursued, preferably during the second trimester. The threshold for surgery in pregnancy is higher but the indications are the same as those in the non-pregnant population - obstruction, perforation, abscess, severe hemorrhage, or acute refractory disease.

Medication Use and Safety

Medication safety is a significant concern among patients who are considering conception or pregnancy.[50] Data from the PIANO (Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes) registry as well as European registries has shown that most IBD drugs do not result in adverse outcomes including congenital malformations, spontaneous abortion, preterm birth, low birth weight, increased infections during the child's first year of life, or inability to achieve developmental milestones.[27,51]

Here we will discuss the various medication categories in depth.

5-aminosalycylic acid

5-aminosalicylic acid (5-ASA) agents are low risk during pregnancy and should be continued.[52,53] Sulfasalazine does interfere with folate metabolism and carries a theoretical risk of interfering with DNA and RNA synthesis in the fetus, increasing the risk of neural tube defects. However, sulfasalazine can be continued throughout pregnancy along with folic acid supplementation at an increased dose of 2 mg per day.[54]

Corticosteroids

Corticosteroids may be necessary for disease flare management during pregnancy, but this is not without risk. Children born to mothers who had intrapartum exposure to corticosteroids or in the three months prior to conception were found

to be at increased risk for preterm birth, small for gestational age, low birth weight, intrauterine growth restriction and neonatal intensive care unit admission.[55] Steroids should be used at the lowest dose and shortest duration possible. Due to its high first-pass metabolism, budesonide is considered lower risk in pregnancy.

Methotrexate

Methotrexate use during pregnancy is associated with spontaneous abortion and embryotoxicity and must be discontinued at least three months prior to conception.[56] This is the only IBD medication to date that is absolutely contraindicated in pregnancy due to its greater than acceptable risk.

Thiopurines: 6-mercaptopurine and azathioprine

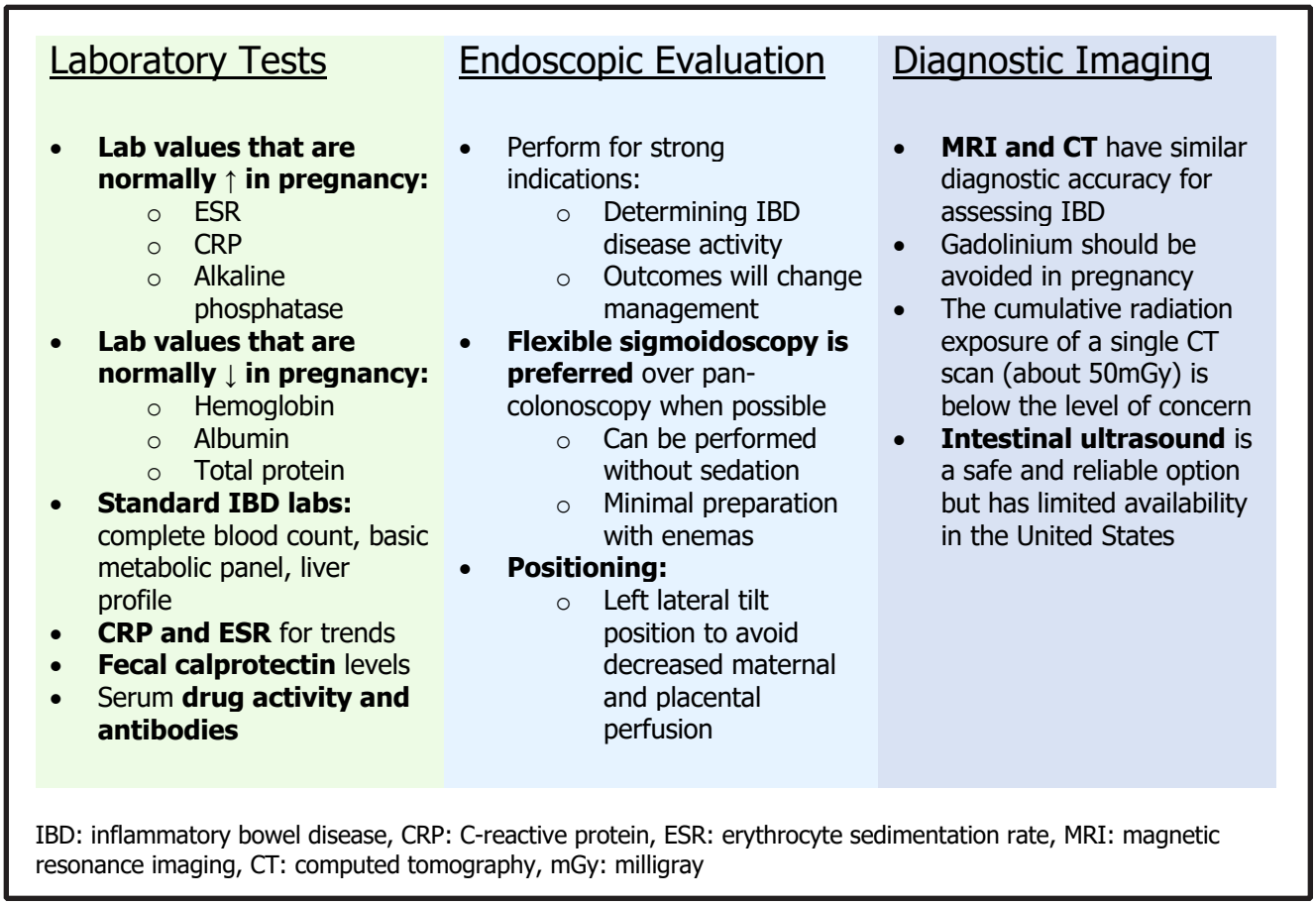
Patients who are taking thiopurines pre-conception to maintain remission can continue on their regimen through pregnancy. Data on thiopurines from the PIANO registry has shown no increase in spontaneous abortions, congenital malformations, low birth weight, preterm birth, rates of infection in the child, or developmental delays.[57-61] Notably, there may be an increased incidence of intrahepatic cholestasis of pregnancy with thiopurine use.[62] Thiopurines should not be started in pregnancy given small but unpredictable risk of leukopenia and pancreatitis as well as slow onset.

Biologic Therapies

Intrapartum use of biologic therapies does not worsen pregnancy or neonatal outcomes, including the risk for intensive care unit admission, infections, and developmental milestones.[51,57] These medications can be continued throughout pregnancy. Pre-pregnancy weight should be used for dosing. Changes in drug levels during pregnancy are negligible and do not warrant closer monitoring during this time.[63,64]

Anti-tumor necrosis factor (anti-TNF) agents used in IBD, including infliximab, adalimumab,

Figure 1. Management of Inflammatory Bowel Disease Flare During Pregnancy



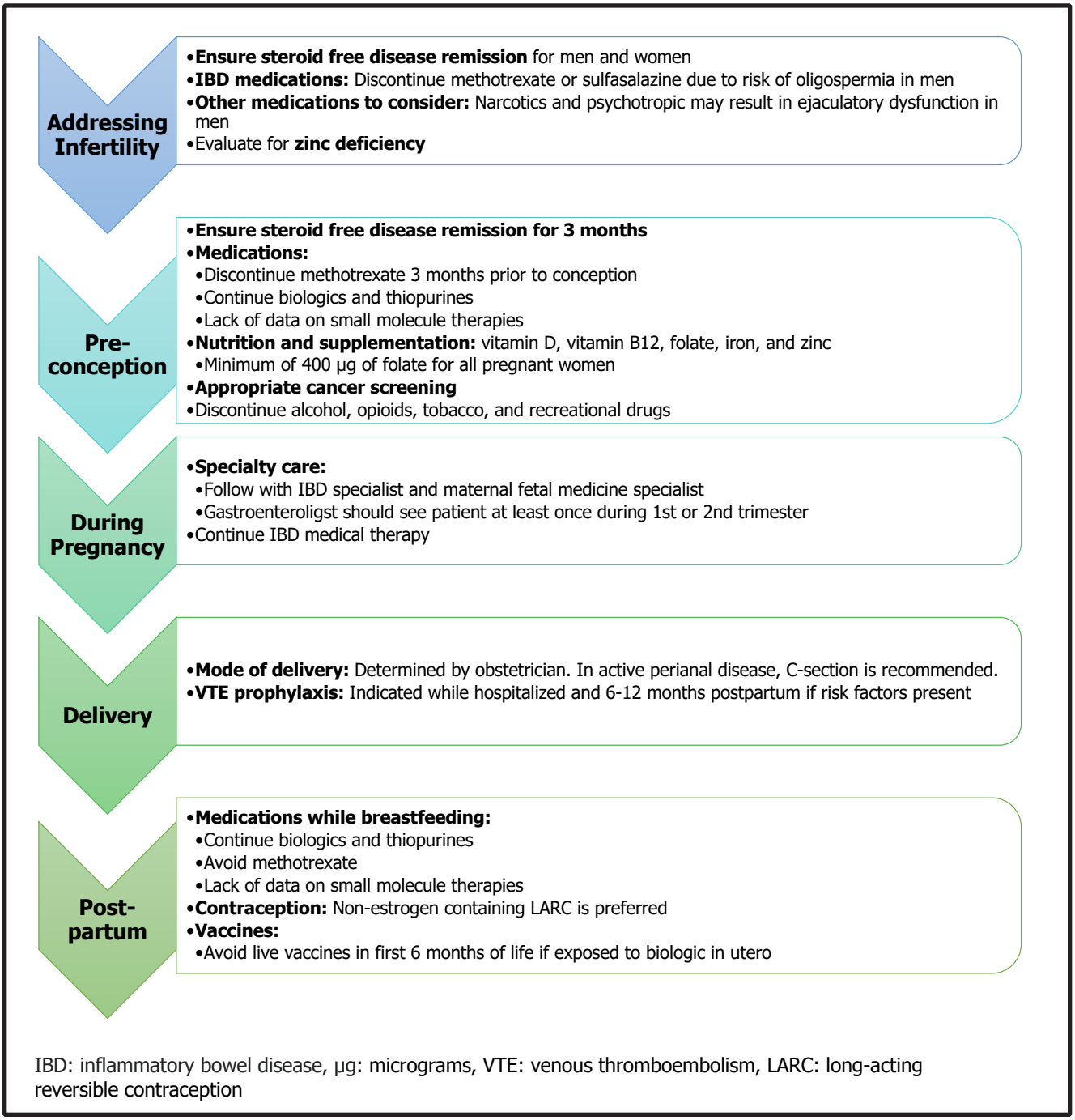
IBD: inflammatory bowel disease, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, MRI: magnetic resonance imaging, CT: computed tomography, mGy: milligray

certolizumab, and golimumab, are low risk for pregnant patients and their offspring. Dosing can continue throughout pregnancy.[65,66]

Natalizumab and vedolizumab are integrin receptor antagonists and are also low risk in pregnancy.[67,68-70,51] While vedolizumab does carry a more favorable side effect profile compared to anti-TNF agents, a study comparing outcomes in anti-TNF and vedolizumab exposed pregnancies found that there was no difference in rates of prematurity, live births, congenital anomalies, or miscarriages.[71]

Ustekinumab, an interleukin-12/23 antagonist, can also be continued during pregnancy; health

Figure 2. Checklist for IBD Management Before, During and After Pregnancy



IBD: inflammatory bowel disease, µg: micrograms, VTE: venous thromboembolism, LARC: long-acting reversible contraception

outcomes in the exposed mother and child are comparable to those of the general population.[51,72,73]

Small Molecule Drugs

Unlike monoclonal antibodies which began active transfer across the placenta in the second trimester, small molecules can cross the placenta during the first trimester.

Tofacitinib, a janus kinase (JAK) inhibitor, and ozanimod, a sphingosine-1-phosphate receptor agonist, are both approved for use in ulcerative colitis.[74,75] At this time, there is inadequate data to make conclusions on their safety in pregnancy.

Delivery

Mode of Delivery

The obstetrician should determine the mode of delivery. The two scenarios where the patient's gastroenterologist suggests method of delivery is if the patient has active perianal disease or a history of ileal pouch anal anastomosis (IPAA). In these situations, a C-section may be recommended due to the risk of fourth-degree laceration and anal sphincter dysfunction with vaginal delivery.[76,77,78,79] Anorectal motility may be impacted by IPAA construction and vaginal delivery independently of each other. It is therefore suggested that vaginal delivery be avoided in patients with a history of IPAA to avoid compounding the risk.

Anticoagulation

The incidence of venous thromboembolism (VTE) is elevated in the pregnant IBD patient during pregnancy, and up to 6-12 weeks postpartum, compared to pregnant non-IBD patients.[80,81] VTE prophylaxis is indicated during hospitalization and potentially thereafter depending on the patient's individual risk factors. Unfractionated heparin, low molecular weight heparin, and warfarin are safe for breastfeeding women.[4,82]

Postpartum Care of Mother

In the first six months postpartum, one third of patients will experience a postpartum flare.[83,84] De-escalating IBD therapy during or immediately postpartum is a predictor of a postpartum flare.[84] As long as there are no signs of infection, biologic therapies can be resumed as scheduled 24 hours after a vaginal delivery and 48 hours following a C-section.[4,85]

Non-steroidal anti-inflammatory drugs (NSAIDs) can be used for pain relief but for the shortest duration possible to avoid disease flares. Opioids should be utilized for the shortest duration possible as well, particularly in the breastfeeding woman, to avoid infant sedation.[86]

Contraception

Contraception should be addressed postpartum. Non-estrogen containing, long-acting reversible contraception (LARC) is preferred due to the increased risk of VTE associated with exogenous estrogen use[87,88] and the reduced efficacy of oral contraceptives in those with active small bowel inflammation and prior small bowel resection.[4,89]

Post-Delivery Care of Baby

Breastfeeding

All biologics and thiopurines used for IBD management are present in low to undetectable levels in breastmilk and can be continued without interruption.[90,91] There is no data to support a "pump and dump" method after an injection or infusion of a biologic.

On the other hand, the active metabolite of methotrexate is detectable in breastmilk and most sources recommend not breastfeeding on methotrexate.

5-ASA therapies can be continued in breastfeeding as well. Alternatives to sulfasalazine are preferred since the sulfapyridine metabolite transfers to breastmilk and may cause hemolysis in infants born with a glucose-6-phosphate dehydrogenase (G6PD) deficiency.[91]

There is not enough data on small molecule therapies in IBD at this time to support breastfeeding safety.

The transfer of steroids to the child via breastmilk does occur but at subtherapeutic levels.[4] Budesonide has high first pass metabolism and is low risk during breastfeeding.[92,93]

Vaccines and Infection Risk

If a child's mother was exposed to any biologic agents (excluding certolizumab) during the third trimester, any live vaccines should be withheld in the first six months of life. In the United States, this currently only applies to the vaccine against rotavirus, administered at 2 months of age.[4,94] All other vaccines can proceed on schedule as indicated by the Center for Disease Control and Prevention guidelines. Children are demonstrated to achieve immunity even when exposed to IBD therapies through breastmilk.[95]

A child with in utero exposure to biologic therapies does not have an increased risk of infection in the first year of life when compared to the general population. This further applies to biologic exposed children attending day care, a setting that is known to increase incidence of infection in children.[96]

Developmental Milestones

Infant exposure to biologics and thiopurines either in utero and/or through breastmilk has not been shown to result in any developmental delays. The PIANO study measured developmental milestones at 48 months from birth and found no differences when compared to validated population norms.[51] This again holds true when looking at childhood development up to 7 years of age in patients born to IBD-affected mothers.[97]

CONCLUSION

Pregnancy and fertility should be addressed in all IBD patients considering conception. Fertility, pregnancy outcomes for the mother, and the health of the offspring are all impacted by disease activity. Maternal and fetal outcomes are largely dependent on appropriate IBD care pre-conception and achieving steroid-free remission. Data from the PIANO registry has demonstrated that IBD medications, with the exception of methotrexate, can be used without interruption during pregnancy and breastfeeding. There is inadequate data on small molecule therapies at this time to recommend their use.

Fertility in men and women is also negatively impacted by disease activity. While certain medications may be implicated in oligospermia or sperm dysfunction in men, these effects are reversible with discontinuation of the drug. ■

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