1) Are thiopurines and anti-TNF-alpha drugs safe to use during pregnancy in patients with IBD?

IBD primarily affects women during their reproductive years with a peak incidence in the third decade of life. The risk of a disease flare during pregnancy is about 30% and is similar to non-pregnant patients. Active disease during pregnancy predisposes to adverse outcomes including miscarriage, pre-term delivery, small for gestational age fetus and possibly fetal malformations. These risks are believed to be higher than the risks associated with any IBD-related therapy with the exception of those in category X (methotrexate and thalidomide). In this retrospective, multicenter study from Spain, investigators evaluated the risk of adverse pregnancy outcomes based on the exposure to thiopurines (TP), biologics, both or neither (control group) in 571 pregnancies in 421 IBD patients. As expected, there were significant differences between groups as far as disease type, behavior and severity. Only 29 patients received biologic therapy alone or in combination with thiopurines whereas a surprisingly small number of control patients were treated with steroids (9%). The rate of unfavorable pregnancy outcomes was significantly lower among patients receiving TP compared to biologics or controls (22% vs. 35% and 32% respectively). In multivariate analysis, treatment with TP was the only predictor of favorable outcome whereas maternal age > 35 at conception was the only predictor of adverse outcomes. There was no evidence of increase fetal malformations risk among TP or biologic users during conception or pregnancy. Pregnancies in which anti-TNF therapy was discontinued during the first trimester had a higher rate of unfavorable outcomes including miscarriage compared to those who continued biologic therapy throughout pregnancy (69% vs. 25%, p< 0.05) and this was associated with increased disease activity.

Comments: Overall the data from this study is reassuring for both patients and physicians caring for pregnant patients with IBD. Even if the protective effect of thiopurines for adverse pregnancy outcomes is difficult to explain (and likely related to confounders), the study provides reassurance in regards to the use of immunosuppressive drugs during conception and pregnancy. Furthermore, there was some evidence that discontinuing biologic therapy early may be associated with increased disease activity and worse outcomes. Unfortunately, thiopurines continued to be labeled as class D based on the FDA classification. This study along with several others published previously should provide evidence regarding the safety and potential benefit of these drugs during pregnancy. As an associated editorial points out, the goal of every physician caring for pregnant patients with IBD should be to minimize disease activity by using low risk medications at their disposal. Based on the data presented here, both thiopurines and anti-TNF therapy fit the bill.

2) Effects of discontinuing anti-TNF therapy during pregnancy in IBD patients

Anti-TNF agents are monoclonal antibodies or fragments thereof. Since they are built on a IgG scaffold, intact antibodies are actively transported across the placenta, particularly in the third trimester. Given the unknown safety profile of biologics in the new-born, recommendations were made to discontinue anti-TNF therapy (with infliximab and adalimumab) before week 30 in patients with stable disease. The authors of this paper investigated the outcome of this intervention in a small group of patients with IBD. Over a period of 5 years, they followed 31 pregnancies in 28 women, 18 with infliximab (IFX) and 13 with adalimumab (ADA). The majority of patients had Crohn’s disease and was subjectively in remission. About a third of them were using concomitant thiopurines. Five patients continued IFX throughout their pregnancy, while the others discontinued either IFX or ADA sometime during the second trimester. The majority of patients remained in remission after stopping the biologic and was able to resume the drug at various intervals post-partum without major complications or loss of response. There were 3 miscarriages (within the expected range) but no congenital abnormalities were reported. Among the 18 newborns in whom cord blood drug levels were measured, the vast majority had detectable levels of anti-TNF agents. However, the levels were significantly higher in the offspring of mothers who continued anti-TNF therapy through the third trimester compared to those who discontinued before week 30. Drug levels in the mother were not available. No immediate adverse effects were seen in any of the newborn children. The authors conclude that discontinuing anti-TNF therapy during the third trimester appears safe for the mother.

Comments: this is a small study that adds to the body of literature regarding the safety of biologics during pregnancy. In addition, it appears that holding these drugs for up to 30 weeks around delivery is not associated with loss of response or intolerance in the majority of patients who resumed these agents post-partum. However, regardless of the interval from the last dose to delivery, the majority of newborns still had detectable levels of anti-TNF drugs in the cord blood. Since the safety threshold and durability of these levels in the infant is unknown, one has to wonder if stopping the biologics early has any merit for the safety of the child. It has been recommended that children of mothers who have been exposed to these biologics during the third trimester do not receive live vaccines (such as BCG or Rotavirus) for at least 6 months post-partum. Whereas the same recommendation should apply now to all offspring of females who received biologics at any time during pregnancy is unknown. Also, there appears to be no difference between injectable and infused, complete anti-TNF antibodies and the presence of detectable levels in the cord blood. It has been shown, however that certolizumab pegol, which is an immunoglobulin Fab fragment coupled to PEG does not cross the placenta owing to its size and the absence of the FC fragment.

3) Placental transfer of anti-TNF agents in pregnant patients with IBD.

Women with IBD face the dual challenge of being healthy enough to conceive and carry a pregnancy full term while at the same time protecting the fetus from the potential adverse effects of medical therapy needed to keep the disease under control. Biologic agents are effective, but they have to be continued until late in pregnancy to avoid the risk of a flare with its potential dire consequences. Although they are classified as pregnancy category B (safe), anti-TNF monoclonal antibodies tend to cross the placenta particularly during the third trimester and their effect on the newborn is unknown. The aim of this study was to determine the cord blood and infant serum concentration of 3 anti-TNF agents in 31 women who received either infliximab (IFX), adalimumab (ADA) or certolizumab pegol (CZP) during pregnancy. All women continued the biologic through the third trimester. About half of the deliveries occurred by C-section. There were no reported birth defects or serious adverse outcomes related to medication use in any of the pregnancies. The cord or infant level of two of the biologics, IFX and ADA were on average 1.6 – 1.8 times higher at birth than the respective levels in the mother. In addition, levels of IFX and ADA were detectable in the infant for up to 7 months. In contrast, CZP levels in the newborn were 25 times lower than in the mother and, in many cases undetectable. No PEG was detected in any of the infant plasma. There was no association between the time from dose to birth and the drug levels in the infant for either IFX or ADA although the sample size is very small.

Comments: This study confirms what was already known about the pharmacokinetics of monoclonal antibodies in pregnant patients and their offspring. However, the effect of detectable biologics in the newborn is unclear. In the much larger PIANO registry (Mahadevan et al. – DDW ’12), infants exposed to combination therapy with an immunomodulator and a biologic had a slightly higher incidence of infections in the first year compared to those exposed to monotherapy. There is also a much publicized single report of a child developing disseminated BCG infection following vaccination two months after birth to a mother exposed to biologic during pregnancy (Cheen et al. – Journal of Crohn’s and Colitis ’10). As a result, children exposed to IFX and ADA during the third trimester should not receive live vaccines in their first 6 months of life. In the US, the only relevant vaccine is Rotavirus which is usually administered at 8 weeks. In addition, women in stable remission should probably withhold IFX or ADA after week 30 to mitigate the transplacental transfer. The alternative would be to use CZP in women who are pregnant or contemplate pregnancy and need to start an anti-TNF agent. Switching a pregnant patient from a different biologic to CZP solely for this purpose, however, would be ill advised. Finally, it has been shown that the level of any of the anti-TNF agents described above is either undetectable or extremely low in the breast milk of women who are currently under treatment with these drugs (1/100th to 1/200th the level in the mother). Therefore all 3 biologic agents should be safe to use by nursing mothers. In turn, breast feeding was associated with a lower risk of developing IBD in the offspring so this should be encouraged. The much larger, prospective, PIANO registry is currently enrolling and preliminary data should be available soon. This landmark study supported by the CCFA should be able to provide us with much more reliable answers to a number of questions about benefits and risks of biologic and immunomodulator therapy both during pregnancy and long-term after birth.