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Inflammatory Bowel Disease Therapies and Pregnancy and Neonatal Outcomes: Results from the PIANO Registry

Florence-Damilola Odufalu

Uma Mahadevan

Pregnant women with inflammatory bowel disease (IBD) are at higher risk for adverse pregnancy outcomes, and disease activity is a major determinant of these adverse outcomes. Controlling disease activity prior to conception and through the postpartum period is critical to improve health outcomes for both mother and child. However, due to misconceptions and a lack of robust safety data, discontinuation of IBD therapies during pregnancy can occur. Effective management of pregnant IBD patients is complex and requires a multidisciplinary approach. This update reviews the results from the prospective, 13 year Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry addressing common questions and concerns regarding IBD pregnancy and therapeutics, and maternal and fetal outcomes with respect to disease activity, infections, and infant growth and development.

INTRODUCTION

The peak age of onset of inflammatory bowel disease (IBD) is during the third decade of life, overlapping with reproductive years. Women with IBD are more likely to have adverse pregnancy complications, further exacerbated by active maternal disease.[1] Although most patients with IBD have uncomplicated prenatal and postpartum courses, active disease complicates approximately 30% of pregnancies.[2] Therefore, controlling maternal disease activity throughout pregnancy with stable pharmacologic therapy is a high priority. However, there remains concern about the safety of IBD therapies with respect to both mother and child. Medication non-adherence remains high in the pregnant IBD population and has the potential to worsen outcomes.[3] This update highlights maternal and neonatal outcomes from the large multicenter prospective cohort, Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO).[4]

The recent publication of the PIANO registry data in *Gastroenterology* is a product of over a decade of research and 1500 pregnancies among women with IBD followed prospectively throughout pregnancy and the first four years of the infant's life. Patients were enrolled across the U.S. through the Crohn's Colitis Foundation Clinical Research Alliance. The primary objective of the PIANO registry is to address whether exposure to thiopurines, biologics and combination therapy

Florence-Damilola Odufalu, MD Uma Mahadevan, MD University of California San Francisco, San Francisco, CA

(monoclonal antibodies and thiopurines) in pregnant women with IBD leads to an increase in specific adverse outcomes.

Pregnancy Outcomes

The investigators from the PIANO registry studied adverse outcomes during the prenatal and postpartum period. The study enrolled 1712 pregnant women with IBD, including Crohn's Disease (CD), Ulcerative Colitis (UC) and IBD indeterminate. Of those, 1490 completed pregnancy with 1431 live births. The cohort had a higher number of patients (62%) with Crohn's Disease. This is in comparison to the prevalence of 37 to 246 cases per 100,000 persons for ulcerative colitis and from 26 to 199 cases per 100,000 persons for Crohn's Disease.[5] The median disease duration was 8.3 years. The cohort included women with exposure to infliximab, adalimumab, certolizumab pegol, golimumab, natalizumab, vedolizumab, ustekinumab, mercaptopurine, azathioprine, or combination therapy.

Pregnancy outcomes examined included spontaneous abortion (SAB), preterm birth (<37 weeks), stillbirth, intrauterine growth restriction (IUGR), small for gestational age (SGA), low birth weight (LBW) (<2500 g), abruptio placenta, eclampsia/preeclampsia, cesarean delivery, Neonatal Intensive Care Unit (NICU) stay at birth and congenital malformations. Adverse pregnancy outcomes are outlined in Table 1. Overall, there were no differences in rates of pregnancy complications comparing those exposed to biologics and thiopurines and those not exposed to these medications. Similar findings were observed even when comparing pregnancies in mothers with IBD without any IBD medication exposure, biologic exposure excluding the 3rd trimester, and biologic exposure throughout pregnancy and through birth. This highlights that sustained IBD therapy throughout the duration of pregnancy does not increase maternal or infant complications.

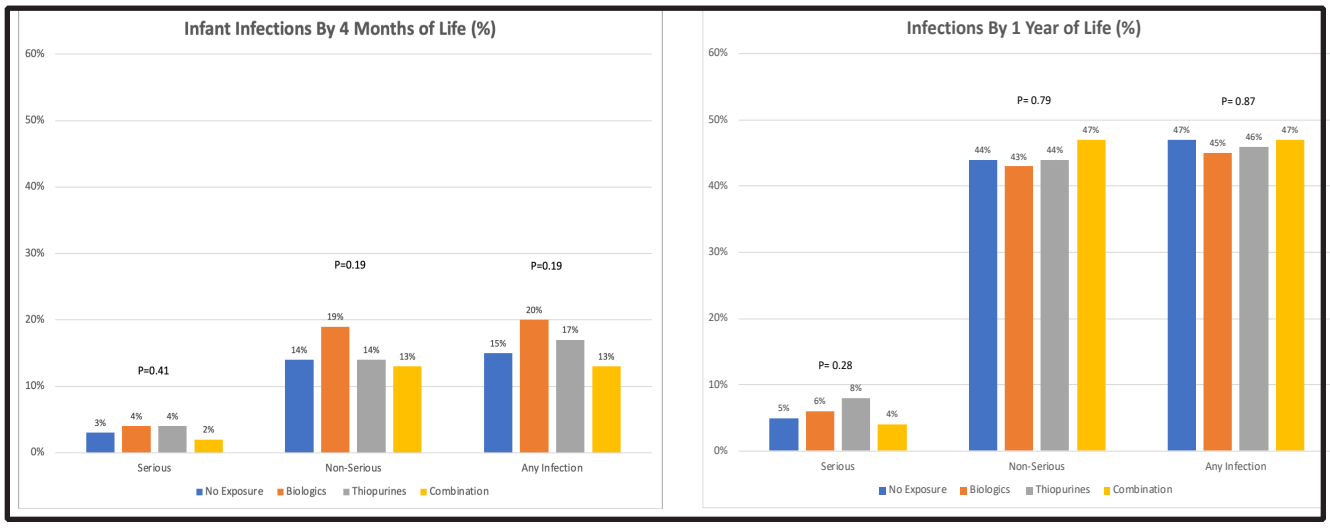
There has been a rapid increase in Cesarean delivery since 1996, with rates in the general population as high as 33%.[6] When active perianal disease is present (usually in CD), there is up to a 10-fold increased risk for fourth-degree laceration and elective Cesarean delivery is recommended.[7] In the PIANO cohort, Cesarean delivery was observed in 43% of enrolled participants. Women on biologics or on combination therapy had higher rates of Cesarean delivery compared to the unexposed population. Active or severe IBD was the most common indication for Cesarean delivery for women with and without biologic or thiopurine exposure. However, in women on combination therapy, perianal disease was the most common indication for Cesarean delivery.

Table 1. Pregnancy related complications by drug exposure, controlling for maternal age, steroid use and disease activity

Event	No Exposure (n=379)	Biologics* (n=642)	# Thiopurine (n=242)	Combination** (n=227)
Any Pregnancy Complication^	1.0 (Ref)	1.2 (0.8, 1.7)	1.3 (0.8, 2.0)	0.8 (0.5, 1.3)
Spontaneous Abortion (Only Gestation Ages <= 140 Days)	1.0 (Ref)	1.3 (0.5, 3.3)	1.4 (0.4, 4.2)	1.2 (0.4, 3.8)
Preterm Birth (<37 weeks)	1.0 (Ref)	0.9 (0.5, 1.5)	1.4 (0.8, 2.6)	1.8 (1.0, 3.3)
Small for Gestational Age	1.0 (Ref)	1.1 (0.5, 2.0)	0.5 (0.2, 1.5)	0.7 (0.3, 1.8)
Cesarean Section	1.0 (Ref)	1.3 (1.0, 1.8)	1.3 (0.9, 1.9)	1.7 (1.1, 2.5)
NICU at Birth	1.0 (Ref)	1.1 (0.7, 1.9)	1.2 (0.6, 2.2)	1.5 (0.8, 2.8)
Congenital Malformations	1.0 (Ref)	1.5 (0.9, 2.5)	1.4 (0.8, 2.7)	1.6 (0.8, 3.1)
Any of the Above w/o Considering Cesarean Section	1.0 (Ref)	1.2 (0.9, 1.6)	1.4 (1.0, 2.0)	1.2 (0.8, 1.8)

*Biologics defined as anti-TNFa, anti-integrin, anti-IL 12/23 #Thiopurine (azathioprine or 6-mercaptopurine) **Combination defined as biologic + thiopurine ^Defined as any self-reported pregnancy complication (excludes intrauterine growth restriction, cesarean section or pre-term delivery) Logistic regression models controlling for maternal age, steroid use, and disease activity

Figure 1. Rates of infection over the first 12 months of life by drug exposure among live births



Disease Activity

The PIANO registry explored the impact of disease activity on both maternal and infant outcomes. UC mothers had significantly lower rates of remission per trimester and higher rates of flares compared to CD mothers. This finding is consistent across several studies as discussed in a meta-analysis of 14 studies, which found a significantly higher risk ratio of active disease during pregnancy in patients with UC who commenced pregnancy with active disease (55%) compared with those whose disease was in remission at conception (36%) (risk ratio, 2.0; 95% confidence interval, 1.5–3; $P < .001$).[8] The higher rates of increased disease activity during pregnancy in UC compared to CD is interesting and may point to a mechanistic difference in response to the pregnancy state or may suggest the mothers with UC are undertreated compared to CD.

Results from PIANO also determined that the first trimester represents the period with the highest rate of flare. This was more pronounced in women with IBD not on therapy. Prior studies also correlate with these findings, demonstrating that discontinuation of anti-TNF before week 24 increases the risk of disease flare.[9,10] In the PIANO cohort, higher rates of disease activity was associated with risk of spontaneous abortion (HR 3.41, 95% CI 1.51-7.69). These findings highlight that priority should be given to treating active disease in pregnancy and the critical role of preconception planning and a stable therapeutic regimen for improved pregnancy outcomes.

Infections

Pregnancy represents a unique immunologic state and dysregulation of immunological mechanisms is increasingly implicated in the pathogenesis of preterm birth, infections and other pregnancy-related complications.[11] Consequently, pregnancy presents many challenges for making decisions on how to approach and prevent infectious diseases. In pregnant women with IBD, there is a lack of data regarding rates of infections for mother and child with exposure to immunosuppressive therapies.

Birth, and the first few months of life, represent a critical time where children have vulnerable immune systems and are more susceptible to infection. In this critical time, part of the infant immunity is reliant on maternal antibodies that cross the placenta, and most of this transfer occurs during the third trimester. With the exception of certolizumab, biologics (monoclonal antibodies) actively cross the placenta.[12,13] The effect of biologics presence in the neonate and the effect on the developing immune system raises several concerns about infection risk. Results from the TEDDY study suggested exposure to anti-TNFα drugs *in utero* does not increase the risk of severe infections in children born to mothers with IBD.[9] Outcomes from the PIANO cohort confirmed that there was no increase in serious, non-serious or any infection in the first year of life in infants with thiopurine, biologic or combination therapy exposure (Figure 1). The majority of infections were

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non-serious, consisting primarily of otitis media and upper respiratory infections. Serious infections were rare, consisting of febrile illnesses requiring antibiotics, sepsis or hospitalization. Preterm birth was the only independent risk factor for infection (OR 1.73, 95% CI 1.19-2.51). Infection rates did not differ by individual biologic agent.

In nursing mothers receiving biologic therapy, very low levels of drug are detected in breastmilk.[14,15] When compared to infants that were not breastfed, breastfed infants in PIANO with biologic exposure did not have higher rates of infection or reduction in achievement of developmental milestones.[15]

Daycare attendance among the general population is associated with an increased risk of serious and non-serious respiratory and gastrointestinal infections in the first years of life. Through the PIANO cohort, longitudinal information was examined in mother-child pairs. Overall, as expected, children in daycare had a higher rate of any infection. However, there was no difference in serious infections compared to those not in daycare. Biologic use was not associated with increase in infection in children attending daycare.[16]

It is well established that IBD patients on immunosuppression, particularly on combination therapy, are at risk for reduced or inadequate vaccine response.[17] Data from the PIANO cohort has shed light on the long-term outcomes of vaccine response in infants with *in utero* exposure to biologics (monoclonal antibodies), thiopurines and combination therapy. In a study by Beaulieu, Ananthakrishnan et. al, data from infants born in the PIANO cohort demonstrate that the rates of adequate serologic response to *Haemophilus influenzae* B (HiB) and tetanus vaccines were similar among infants born to women on biologic therapy compared to those who were not exposed during pregnancy.[18] There was also no association between cord blood or infant serum concentrations of biologics and adequacy of vaccine titers.[18]

Subgroup analysis of the TREAT registry demonstrated that anti-TNFα may be associated with increased maternal complications including infection.[19] The rate of serious infections among those who had received infliximab was significantly higher than those who were not treated with infliximab (1.37 per 100 patient-years vs .65; RR [95% CI], 2.15[1.442–3.210]; P < .001), however this was confounded by disease activity as patients in the infliximab-treated group were more likely to be receiving prednisone, immunomodulators, and narcotic analgesics.[19] In the PIANO cohort, maternal postpartum infections were rare. The incidence of perineal trauma and poor wound healing is not significantly different in the IBD patient population compared to the general population.[20]

Infant Growth and Development

Epidemiological studies have shown that infants exposed to stress in the womb are at higher risk of impaired cognitive development and growth restriction. A recent study by Stoye et al. examined the impact of maternal stress and found that chronic maternal stress state in pregnancy is associated with microstructure and structural connectivity of the newborn amygdala, a region of functional importance for early social development and emotion regulation.[21]

Studies in childhood growth and development are often difficult to ascertain causality, as there are several host factors and socioeconomic factors that contribute to growth and development. The PIANO study examined differences in infant growth and developmental milestones at 12 months of age by drug exposure. Overall, there were no differences in height or weight outcomes by drug exposure, or in odds of being very low for length or weight, controlling for preterm birth and maternal disease activity. There were also no differences in developmental milestones in the first year of life by exposure status within the cohort or compared to validated Ages & Stages Questionnaire norms. However, scores of biologic and/or thiopurine exposed infants were slightly higher than the general population in some categories.[22]

Congenital Malformation

The risk of congenital malformations related to biologic and thiopurine exposure were addressed in the PIANO cohort. Of the 1431 live births observed, 133 (9%) infants had congenital malformations. No pattern of congenital malformations was suggested based on IBD and medication exposure. The observed rate of congenital malformations

was higher than reported in national observation estimates of congenital malformation prevalence data, but not different by drug of exposure. This increased rate is likely secondary to the close monitoring of each participant over one year and strict inclusion and classification of congenital malformations.[23]

SUMMARY

Pregnant women with IBD are at higher risk for adverse complications of labor and delivery. This risk is heightened by active disease, emphasizing the importance of controlling disease activity prior to conception and through delivery. However, there remains concern about the safety and approach for managing IBD therapies during pregnancy, as well as the impact on the developing fetus and long-term outcomes. The PIANO registry clarified this risk to provide IBD patients and providers important safety information and guidance. The PIANO registry provides clear long-term safety data on mother and child demonstrating that biologic, thiopurine or combination during pregnancy is not associated with increased adverse maternal or fetal outcomes at birth or within the first year of life, and likely the first four years of life as well. With this collection of safety data, providers can advise that women with IBD on biologics, thiopurines or combination therapy should continue this regimen throughout pregnancy and the post-partum period to maintain remission for the health of the mother and the child. Future studies in PIANO will use the existing infrastructure to look at new therapies for IBD and will continue to follow children out to 18 years of age ■

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