Parental IBD and long-term health outcomes in the offspring

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ABSTRACT

For decades, the research on reproductive consequences in women with inflammatory bowel disease (IBD) has focused on short-term outcomes, including adverse pregnancy outcomes (e.g., abruptio placenta, placenta previa, preeclampsia/eclampsia) and adverse birth outcomes (e.g., small for gestational age, preterm birth and congenital malformations). The long-term health outcomes of the children of parents with IBD have been studied to a much lesser extent and there is a critical research gap in understanding the influence of parental IBD on long-term outcomes. In this review, we propose the reasons for this lack of evidence and highlight the weakest areas of research on the impact of parental IBD on offspring health. We will focus on health outcomes in children of parents with IBD from an age of 1 year through childhood, adolescence, and adulthood.
INTRODUCTION

The incidence and prevalence of inflammatory bowel disease (IBD) is increasing and during the last 50 years, both ulcerative colitis (UC) and Crohn’s disease (CD) have become two of the major gastroenterological problems in the westernized world\textsuperscript{1,2}. As the trend in life expectancy increases, patients with IBD will constitute a growing proportion of patients with chronic diseases and specialized health care service needs.

One of the important clinical care and research areas, in the expanding population of young women and men with IBD, are the concerns related to reproduction. Patients often question their ability to conceive, plan a pregnancy, cope with disease during pregnancy and ensure safety of medications during pregnancy and nursing. Additionally, patients worry about the impact of IBD and IBD medications on short and long-term health consequences in the offspring. When it comes to “short-term” and “long-term” health consequences in the offspring, there exist no strict definitions; the concept “short-term” health outcomes normally include adverse pregnancy outcomes (for instance the risk of ectopic pregnancy, spontaneous abortions and preeclampsia), and adverse birth outcomes (for instance the risk of growth retardation, preterm birth and congenital malformations recognized during the first year of life). “Long-term” outcomes, on the other hand, normally include studies examining the risk of diseases in the offspring during childhood, adolescence, and adulthood.

For decades, a large part of reproductive research in women with IBD has focused on adverse birth outcomes\textsuperscript{3-9}. This is a continuously important area for research as adverse short-term birth outcomes, such as small for gestational age and preterm birth, are strong predictors for child morbidity and mortality, and because the underlying mechanisms (related to, for instance,
gestational hormones, specific inflammatory pathways, and medications) are, for a large part, unknown.

Much less attention has been given to the association between a possible impact of maternal or paternal IBD on long-term child outcomes. We know that offspring of parents with IBD have an increased risk of having IBD themselves\textsuperscript{10,11}, but otherwise we know very little about whether parental IBD itself, or the medications used to treat it, might influence the probability of the offspring developing diseases during childhood, adolescence, and adulthood. Yet, why should there be a negative impact of parental IBD on the health of the offspring? In addition to genetic susceptibility to IBD, there are many other reasons that offspring of IBD parents may be at a greater risk of developing diseases later in life. Common genetic and environmental risk factors may explain concurrent increases in certain diseases during childhood and adulthood and some chronic diseases share genetic overlap to IBD\textsuperscript{12}. Several studies have suggested an association between IBD and various autoimmune diseases\textsuperscript{12-16}. Autoimmune endocrine diseases, for example, are polygenic and it has been known for decades that they recur within families\textsuperscript{17-20}. Other important factors for long-term health of the offspring might be related to in utero exposure to maternal medication during pregnancy and/or paternal use of medications around the time of conception. One of the most important historic examples of an association between in utero drug exposure and adverse long-term consequences in the offspring was the use of diethylstilbestrol before 18 weeks of gestation that in female fetuses caused 1-1.4/1000 risk of the development of vaginal adenocarcinoma\textsuperscript{21}. From a maternal perspective, the topic of medication safety during pregnancy has been an area of major interest as most drugs and metabolites cross the placenta to the fetal circulation\textsuperscript{22-26}, but research has mainly focused on short-term consequences in the offspring. From a paternal perspective, some medications have been suspected to have mutagenic effects on
developing sperm and/or direct toxicity via seminal fluid, and many studies have linked environmental and chemical exposures in fathers to childhood diseases\textsuperscript{27-37}.

In contrast to former literature, which has concentrated on the association between maternal IBD and short-term outcomes in the offspring, this review will focus on selected aspects related to the association between parental IBD and long-term health outcomes in the offspring. For the purpose of this review, we define long-term outcomes as those occurring in the offspring from the age of 1 year and up to adulthood. We will elaborate on i) the possible reason for the lack of evidence when it comes to long-term outcomes, ii) the associations between maternal IBD and long-term health outcomes in the offspring, iii) the associations between \textit{in utero} exposure to medications used to treat maternal IBD and long-term health outcomes in the offspring, iv) the associations between paternal IBD and long-term health outcomes in the offspring iv) the associations between paternal use of IBD medications around the time of conception and long term health outcomes in the offspring.

\textbf{Why has most of the existing research focused on short-term outcomes?}

Studies on short-term outcomes have been prevalent for number of reasons. It is evident that the general and the immediate health of a newborn child attract much attention, and therefore the risk of adverse birth outcomes in offspring of women with IBD has been studied intensively. Such studies are indeed important as adverse birth outcomes are important prognostic factors for subsequent child morbidity and mortality. The maternal exposures in focus have included the impact of disease activity, the influence of underlying chronic disease and the medications used in the treatment. Also, it has been relatively easy to collect robust datasets on pregnancy and birth outcomes in women with IBD in different hospital and population-based settings. Thus, in most countries,
pregnant women with IBD already attend regular control visits in relevant clinics (obstetrics/gynecology/gastroenterology), and data have been collected during different gestational periods and around the time of giving birth. In such studies, the children have typically been followed until shortly after birth, and regarding the occurrence of congenital malformations the offspring might have been followed within a period of one year after birth in register-based studies.38,39,40.

An important reason for the limited evidence, when it comes to studies on long-term health outcomes, is that it places severe demands for available and appropriate data sets. Studies on long-term health outcomes require access to unselected patient cohorts, where children born to parents with IBD can be followed for long periods of time with regard to development of the diseases of interest during the upbringing. Such data sets must be large in order to provide sufficient statistical power for the outcomes studied, they must ensure complete follow-up of all children to prevent bias, and of course the data sets have to provide valid information on parental diagnoses of IBD, the specific outcomes under study, and important confounders. Such data sets are not easy to get access to, and one could even argue that they do not exist. In many countries not using personal unique identification of all citizens, one of the main challenges is to prevent loss to follow-up because patients move away or die. Additionally, in the future there may be ethical and legal difficulties in conducting long-term research due to varying regulations of consent for data collection. Several of the studies with long-term follow up in children born to parents with IBD have therefore been conducted in the Scandinavian countries11,41-46 where all children can be followed via central registries for long-term disease outcomes, but even such data sets have severe shortcomings. Such shortcomings include lack of detailed information on clinical characteristics such as extent of the disease and disease activity, and an appropriate number of most important confounders. Unfortunately, these methodological challenges may severely limit the feasibility of
accurately studying long-term outcomes. In the 2010 ECCO guidelines for reproduction in IBD, the authors state, “There are no published long term data on infant health outcomes such as neurodevelopment, incidence of childhood malignancies or increased risk for other specific disorders with respect to fetal in utero drug exposure”\textsuperscript{47}. Nothing had changed in the intervening 5 years when the authors of the 2015 ECCO guidelines on the same subject wrote, “The incidence of childhood malignancies or risk for other specific disorders due to long-term fetal exposure to IBD medication remains unknown”\textsuperscript{48}.

**Maternal IBD and long-term health outcomes in the offspring (from the age of 1 year to adulthood)**

The majority of the research has focused on a single outcome disease in the offspring, including the risk of asthma, autism spectrum disorders and the risk of IBD\textsuperscript{42-46} but a few studies focusing on the general health and developmental milestones have been identified\textsuperscript{11,49,50}. Here we refer to studies examining the associations between maternal IBD diagnosed before the time of childbirth and long-term health outcomes in the offspring, including only studies with a control group. Depending on the study design used, different risk estimates are provided across the studies. Studies using a time to event approach will in general thus provide the ratios of “an event with time” – for instance the Hazard Ratios (HR), or Incidence rate ratio (IRR) of IBD from a specific point in time (for instance time of birth) counting until the event/diagnosis of IBD during follow-up. Thus, the HR provides the instantaneous risk ratio at a particular time. On the other hand, the absolute risks or Odds ratios (OR) gives the cumulative risk over a time span. In the interpretation of the estimates the results can to some extend be comparable. Absolute risks have in general not been reported in these studies.
**IBD**

The strongest risk factor for development of IBD is a first degree relative affected with IBD. Moller et al. showed that the IRR for CD in first-degree relatives of patients with CD was 7.77 (95% CI 7.05–8.56) and the IRR of UC in first-degree relative with UC was 4.08 (95% CI 3.81–4.38). The offspring of IBD parents and twins of siblings with IBD are the groups at highest risk\(^1\). In 2017, Jolving et al. published a nationwide register-based Danish study examining the risk of chronic diseases in the offspring of mothers with IBD. In that study the risk of IBD was also estimated. The adjusted HR of IBD in the offspring was 4.63 (95% CI 3.49–6.16) if the mother had UC, and 7.70 (95% CI 5.66-10.47) if the mother had CD\(^1\). This is in accordance with previous literature where similar results in children of mothers with IBD, reported by Moller et al. who showed an increased IRR of CD in children of mothers with CD (6.37 (95% CI 5.07-8.00)) and UC in children of mothers with UC (3.71 (95% CI 3.24-4.25))\(^1\). These findings are also confirmed in different twin studies from Orholm\(^5\), Halfvarson\(^5\) and Thompson\(^5\).

**Asthma**

The risk of asthma is the outcome of interest in a Danish study from 2013 by Andersen et al.\(^4\). The background for examining the association between IBD and asthma is that the two conditions share genetic susceptibility loci\(^1\), and their concomitantly increasing incidence suggests common environmental risk factors in a parent e.g. exposure to antibiotics, endocrine-disrupting chemicals, and smoking. The study however, did not find evidence of an increased risk of asthma in offspring of women with IBD (adjusted IRR 0.97 (95% CI 0.89-1.06)). We did not find other studies addressing this specific long-term outcome.

**Autism spectrum disorders**

Epidemiologic data have suggested that autism spectrum disorders and IBD also may share genetic loci and related environmental risk factors, and additionally both of the diseases have shown
concurrently increasing incidence during the past decades\textsuperscript{54-56}. Some studies have therefore focused on a possible association between maternal IBD and autism spectrum disorders. Keil \textit{et al.} examined the association between maternal IBD and autism spectrum disorders in a case control study from 2010 and found no significantly increased risk (odds ratio (OR) 1.4 (95\% CI 0.8-2.7))\textsuperscript{43}. Three Danish studies have examined the risk of autism spectrum disorders in children born to women with IBD: Atladottir \textit{et al.} found no significant increased risk of autism spectrum disorders in the offspring (for women with CD the adjusted IRR was 0.76 (95\% CI 0.38-1.33) and for women with UC 1.05 (95\% CI 0.68-1.53))\textsuperscript{44}. A case-control study by Mouridsen \textit{et al.} found that maternal UC was associated (but not statistically significantly) with infantile autism (OR 9.1 (95\% CI 0.9-88.8)), however the wide confidence interval indicates the limited number of cases (3 children with infantile autism), and the study should thus be interpreted with caution\textsuperscript{45}. In the study from Andersen \textit{et al.}, the authors found no association with autism spectrum disorders in the offspring (the adjusted IRR was 0.7 (95\% CI 0.5-1.0))\textsuperscript{46}.

\textit{Other chronic diseases and developmental milestones in the offspring}

Freud \textit{et al.} were among the first to study a possible impact of maternal IBD on a wider group of selected long-term health outcomes in the offspring including also non-autoimmune diseases\textsuperscript{49}. A total of 278 children born to women with IBD, and 255,704 without IBD, were followed from birth up to 18 years of age, although no average follow up time was reported. The reported outcomes were hospitalization for cardiovascular, endocrine, hematologic, neurological, respiratory, urinary and gastrointestinal diseases during follow-up, and the authors concluded that maternal IBD during pregnancy was not a risk factor for long-term morbidity of the offspring\textsuperscript{49}. In 2017, Jolving \textit{et al.} examined the risk of 15 different chronic diseases in the 9,238 offspring of mothers with IBD and and 1,371,407 offspring of mothers without IBD\textsuperscript{11}, and this study is so far the most comprehensive on the risk of long-term health problems in the offspring of women with IBD in terms of size of the
study population and length of follow-up. The authors found no evidence of an increased risk of important non-malignant chronic diseases such as diabetes, chronic lung disease and asthma, thyroid disease, epilepsy, schizophrenia/psychoses or personality disorders. Median follow-up was 9.7 years (interquartile range 4.9-15.7) in the children of women with IBD and 13.8 years (interquartile range 7.4-19.9) in the unexposed children. In contrast, a questionnaire study from Dotan et al. concluded that maternal IBD during pregnancy is associated with increased risk of certain medical problems and developmental milestones in the offspring. Four hundred twelve children exposed to maternal IBD in utero were enrolled at 16 +/- 10.8 years and 417 children not exposed at 13.8 +/- 10.3 years. Children born after maternal IBD diagnosis were found to have more neurodevelopmental problems such as gross motor delay, compared to controls of children born before a maternal diagnosis of IBD. The authors speculate that this could be partially attributed to increased preterm birth as well as effects of medication or maternal disease severity. They also speculate that ”potential modulating factors of cognition and neurodevelopment, such as nutritional balance, nutrient interactions, energy balance, fatty acids and trace element availability as well as inflammatory cytokine's effects on development may be affected by IBD in pregnancy and may have important consequences for the fetus.” We did not identify other studies examining a potential association between maternal IBD and offspring neurodevelopmental impairment.

**Summary**

Overall, the studies are hampered by the limited number of children that have been followed and by the limited number of years during follow-up. Although the median follow up times may have been from 9-16 years, many children were younger than this and would not have time to develop chronic diseases. Many chronic diseases and malignancies first present in adulthood. However, the mentioned studies do provide us with some helpful evidence on the risk of non-malignant chronic diseases during childhood and adolescence. Based on the available literature we can therefore not
rule out a possible negative impact of maternal IBD on the long-term health of the offspring, but besides the well-known increased risk of IBD in the offspring, the available results are so far reassuring. To be able to provide more precise results, we need methodologically solid studies, based on a larger number of children who can be followed up throughout childhood, adolescence and adulthood. A summary of the studies describing the association between maternal IBD and long-term health outcomes in the offspring is shown in Table 1.

**In utero exposure to medications used to treat maternal IBD and long-term health outcomes in the offspring (from the age of 1 year to adulthood)**

Many women continue their IBD medications during pregnancy and much of the current literature indicates that the majority IBD medications have little effect on pregnancy outcomes and/or birth outcomes. Increased disease activity, rather than the medications used to treat it, can be most detrimental to a pregnancy and disease flares are associated with preterm delivery and low birth weight. So far, the available literature has suggested that thiopurines and biologics are safe to take during pregnancy and breastfeeding with no increased risk of adverse birth outcomes or neonatal infections up to the first year of life, but only very few studies have examined the consequences of IBD medications taken during pregnancy on the long-term outcomes of the exposed children. Potential effects of *in utero* exposure to IBD medications could include an increased incidence of developmental problems, cancer and chronic disease. Here, we refer to studies examining the associations between *in utero* exposure to IBD medications and long-term health outcomes in the offspring. We will only include studies in IBD patients, with a control group and outcomes of offspring after 1 year of life.

**Biologics**

Infliximab was approved 20 years ago and has been increasingly used during pregnancy, yet there
are only two studies with control groups that examine the long-term outcomes of children exposed to infliximab and other anti-TNFs in utero. In a retrospective study, Chaparro et al. examined the risk of severe infections in infants exposed to anti-TNF in utero versus infants not exposed. All mothers had IBD. In total, 388 with anti-TNF exposure and 453 controls were included. The anti-TNF drugs included infliximab (57.4%), adalimumab (42.3%) and certolizumab pegol (0.3%). Twenty-five percent of infants in the anti-TNF group had also been exposed to thiopurines in utero. A total of 90 children developed severe infections during follow-up (12% in the exposed and 9.7% in the unexposed; P=0.3). Median follow-up time in the unexposed group was 68 months and 47 months in the exposed. Of the exposed group, 34% of severe infections occurred after the first year of life and in the unexposed group, 36% of infections occurred after the first year. The incidence of severe infections in infants exposed to combination therapy (12%) was the same as in infants exposed to anti-TNF monotherapy (11%). There were no neoplasms in any group. Duricova et al. examined 72 children exposed to anti-TNF in utero and 69 children unexposed with a median follow up of 35.1 and 50.4 months respectively. In the exposed group, 75% received infliximab, 25% adalimumab and 37.5% concomitant thiopurines. There was no significant difference in the median rate of infections from birth until the end of follow-up between exposed and unexposed children (p=0.32). In utero anti-TNF exposure was not a risk factor for development of allergies (p=0.98). Additionally, there was no difference in growth or psychomotor development observed between exposed children and controls (p=0.71).

**Thiopurines**

There are only 2 studies of the long-term outcomes of children of mothers with IBD exposed to thiopurines in utero. In a descriptive study without confounder control, Angelberger et al. examined 15 children exposed to azathioprine in utero and during breastfeeding and 15 infants not exposed. Median age of children at time of interview was 3.3 years and 4.7 years, respectively.
There was no difference in mental or physical development, infections or hospitalizations between the groups. There were no neoplasms reported. This sample size is very small though and it is not possible to draw firm conclusions. In another descriptive study without confounder control, De Meij et al.\textsuperscript{65} examined 30 children of mothers with IBD who were exposed to thiopurines \textit{in utero} with a median follow up of 3.8 years. There were no differences from an unexposed group of 340 children in terms of medical or psychosocial health, immunodeficiency or increased infections. There were no neoplasms.

\textit{Other medications}

For 5-aminosalicylates, corticosteroids, cyclosporine/tacrolimus, and antibiotics there are no data on long-term outcomes after \textit{in utero} exposure.

\textit{Summary}

Biologics are relatively new drugs and it may take years until we have reliable results on the association between \textit{in utero} exposure and possible long-term health consequences in the offspring. On the contrary, many IBD medications such as thiopurines, 5-aminosalicylates and steroids have been used for almost 50 years. Although long-term follow-up of exposed children is certainly important and should be feasible, adequate studies are lacking. A summary of the available studies describing \textit{in utero} exposure to IBD medications and long terms childhood outcomes is shown in Table 2.

\textbf{Paternal IBD and long-term health outcomes in the offspring (from the age of 1 year to adulthood)}

The literature describing long-term outcomes of the offspring of fathers with IBD is similar to that of the mothers – it has focused mainly on hereditary risk, asthma and autism\textsuperscript{10,42-46,66}. Here we
focus on studies examining the associations between paternal IBD diagnosed before the time of conception and long-term health outcomes in the offspring, including only studies with a control group.

**IBD**

A recent study from Denmark separated out the risk of IBD in the offspring of fathers with IBD\(^\text{10}\). The authors found that the adjusted IRR for CD in the offspring of fathers with CD was 7.53 (95% CI 6.36–8.91). For fathers with UC, the IRR for having a child with UC was 4.25 (95% CI 3.70–4.87). A second study from Sweden examined parents with one of 34 autoimmune diseases but did not separate out the risk in mothers and fathers. The authors found that the IRR for UC in the offspring of a parent diagnosed with UC was 3.9 (95% CI 3.5 – 4.3) and 6.0 (95% CI 5.4 – 6.7) for CD in the offspring when a parent was diagnosed with CD\(^\text{66}\).

**Asthma**

The incidence and prevalence of asthma has also increased in industrialized countries and asthma and IBD are both immune-mediated diseases that share common genetic loci and environmental risk factors. A large study from Denmark, Andersen et al.\(^\text{42}\), has examined the association between fathers with IBD and the risk of asthma in their offspring, and found no increased risk of asthma in the children of fathers with IBD (adjusted IRR 0.99 (95% CI 0.89-1.09)).

**Autism spectrum disorders**

Autism spectrum disorders are related to IBD in that both may have similar genetic and environmental risk factors. Additionally, autism spectrum disorders have an increasing incidence and prevalence like that of IBD. Several studies have suggested an association between parental autoimmune disease and autism spectrum disorders in the offspring including three recent studies examining an association between paternal IBD and autism spectrum disorders \(^\text{43-46}\). The studies by Atlodittir \textit{et al.}\(^\text{44}\), Mouridsen \textit{et al.}\(^\text{45}\) and Keil \textit{et al.}\(^\text{43}\), all showed no association between CD or UC
in the father and autism spectrum disorders in the offspring. A fourth recent study from Denmark, Andersen et al. 46, that looked specifically at fathers with IBD found no evidence of an association with autism spectrum disorders in their offspring.

Summary

Besides the above-mentioned studies of the risk of offspring developing IBD, autism spectrum disorders or asthma, no other outcomes have been studied. No studies have examined other chronic diseases, acute diseases, malignant diseases, or developmental diseases in the offspring of fathers with IBD. A summary of the studies investigating a link between paternal IBD and long-term outcome in the offspring is shown in Table 1.

Paternal use of IBD medication around the time of conception and long-term health outcomes in the offspring (from the age of 1 year to adulthood)

Compared to the literature that exists on the associations between maternal medication during pregnancy and long-term health outcomes, the available evidence of possible adverse effects after paternal use of medication around the time of conception is very sparse67. This is regardless of the facts that most drugs can be found in semen68, and that direct genetic effects of medications on male sperm cells have long been recognised in animal model studies69. In general there is some evidence that medication used by fathers might influence the offspring due to different mechanisms such as: (i) genetic or chromosomal damage of the spermatocytes; (ii) drugs or metabolites in seminal fluid that might influence sperm maturation and/or produce a direct effect on the uterus; (iii) a systemic effect of the drug or metabolites on the female herself by absorption through the vaginal mucosa27,28,32. As spermatogenesis takes 70–90 days in humans, a 3-month cutoff is most often used in studies looking at the toxic effects of a drug on sperm development and thus potential effect
on the offspring. The impact of paternal use of medications for IBD around the time of conception on the risk of adverse long-term outcomes has to our knowledge only been studied for the use of azathioprine/6-mercaptopurine/methotrexate by Friedman et al. The exposed cohort constituted children fathered by men who used azathioprine/6-mercaptopurine (N=735) or methotrexate (N=209) within three months before conception; and the unexposed cohort constituted children fathered by men who did not use azathioprine/6-mercaptopurine/methotrexate (N=1,056,524). The outcomes studied were malignancies, autism spectrum disorders/schizophrenia/psychosis, and attention deficit hyperactivity disorder. The median follow up time among all exposed children was 6.7 years, and 9.9 years in unexposed children. Due to the small number of outcomes, this was a descriptive study only with no confounder control. However, the results were reassuring with few negative outcomes among the exposed and the authors conclude that there was no negative impact of paternal preconception use of AZA/6-MP/MTX on selected childhood health outcomes.

Summary
To our best knowledge the above mentioned study is so far the only study that has examined an association between paternal use of specific IBD medication around the time of conception and long-term health outcomes in the offspring. IBD medications such as 5-aminosalicylates, steroids and thiopurines have been used for almost 50 years, and long-term consequences after paternal use at the time conception ought to have been an important research area. The use of biologics at the time of conception is definitely also of importance, but since they are relatively new drugs, more time needs to pass before they can be fully investigated.

Conclusion
Although some evidence of the association between maternal IBD and long-term health outcomes in the offspring exists, only a few studies have been conducted on a few specific outcomes, and
mainly on the risk of few chronic diseases in the offspring. The compiled amount of data is indeed very sparse, and there is a great need for more evidence of the association between maternal IBD and the risk of offspring developing specific chronic diseases, acute diseases, malignancies and developmental disabilities during childhood, adolescence and adulthood. Additionally, there is a substantial research gap in studies examining the health consequences in the offspring after in utero exposure to IBD medications, paternal IBD, and paternal medications around the time of conception.

Although research on long-term outcomes is associated with a number of methodological challenges, studies focusing on offspring consequences of parental IBD are indeed warranted. The methodological challenges are such that studies must require i) large data sets to study a wide spectrum of both frequent and rare outcomes with a sufficient statistical precision, ii) no loss to follow-up in the study cohorts, iii) offspring to be followed for a long period of time, and iv) the ability of control for the most important confounders (e.g., smoking, dietary factors, obesity, socioeconomic factors, family history of chronic diseases, medication dosage and duration, exposure to environmental and chemical toxins). As studies on long-term health outcomes need to involve large, population-based cohorts, we recommend collaboration across national borders.

Hopefully, more attention will be given to this area of research as well as a willingness to give these studies priority in the funding process.

It is challenging to reassure patients about the safety of medications for exposed offspring when most studies only look at outcomes within a year of birth. Just as important as pregnancy and birth outcomes are the effects of medications used at conception or in utero on growth, development and risk of diseases in the offspring. It is difficult to be certain about the eventual safety of IBD medications without looking at results in the long-term. Future results on long-term health consequences in the offspring of parents with IBD are vitally important for patients as well as health
care providers. It is up to clinicians and researchers to work together to focus on this issue to provide safe and informed care for our patients.
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Table 1. Studies examining the association between maternal and paternal inflammatory bowel disease and long-term outcomes in the offspring.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study Design</th>
<th>Study population</th>
<th>Study details</th>
<th>Offspring outcomes with relative risk estimates (95% confidence interval)</th>
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</table>
| Joelving et al.\textsuperscript{11} 2017 | Cohort study | All live born children 1989 through 2013 (nationwide Danish data) | 9238 children born to mothers with IBD. 1,371,407 unexposed children born to mothers without IBD. Median follow-up time: 9.7 years among exposed and 13.8 years among unexposed | Type 1 diabetes: aHR=1.12 (0.75-1.68)  
Thyroid disease: aHR=0.97 (0.62-1.53)  
Rheumatoid arthritis: aHR=1.26 (0.99-1.60)  
Ulcerative colitis: aHR=4.63 (3.49-6.16)  
Crohn’s disease: aHR=7.70 (5.66-10.47)  
Epilepsy: aHR=1.00 (0.82-1.22)  
Chronic lung disease, including asthma: aHR=1.05 (0.91-1.21) |
<table>
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<tr>
<th>Study</th>
<th>Design</th>
<th>Sample description</th>
<th>Outcomes</th>
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| Freud et al.  | Cohort study            | All live born children 1991 through 2013 (regional data, Israel)                    | Affective mood disorders:  
aHR=1.19 (0.77-1.82)  
Schizophrenia and other paranoid psychoses:  
aHR=0.72 (0.43-1.22)  
Nervous conditions and personality disorders:  
aHR=0.93 (0.77-1.13) |
|               |                         | 278 children born to mothers with IBD.  
255,704 unexposed children born to mothers without IBD.  
Maximum follow-up 18 years; median follow-up time not given | Endocrine:  
aOR=1.39 (0.34-5.67)  
Hematologic:  
aOR=1.13 (0.41-3.09)  
Neurological:  
aOR=0.67 (0.09-4.71)  
Respiratory:  
aOR=0.71 (0.41-1.22)  
Urinary:  
aOR=0.88 (0.22-3.51)  
Gastrointestinal:  
aOR=0.81 (0.35-1.87) |
<table>
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<tr>
<th>Year</th>
<th>Study Type</th>
<th>Data Source</th>
<th>Number of Patients</th>
<th>Findings</th>
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| 2015 | Cohort | Nationwide Danish data (1977-2011) | 45,780 | Fathers with UC: aIRR for having child with UC 4.25 (3.70-4.87)  
Mothers with UC: aIRR for having child with UC 3.71 (3.24–4.25) |
| 2014 | Cohort | All live born children (1994 through 2009) | 6,700 | Maternal IBD: For autism spectrum disorders aIRR=0.7 (0.5-1.0)  
Paternal IBD: For autism spectrum disorders aIRR=0.9 (0.6-1.3) |
| 2013 | Cohort | Children of mothers with IBD recruited from 7 IBD centers plus unexposed (2004-2009) | 170 | Gross motor delay: 6% among exposed versus 3% among unexposed (p=0.11) |

### Additional Findings:
- Fathers with CD: aIRR for having child with CD 7.53 (6.36-8.91)  
Mothers with CD: aIRR for having child with CD 6.37 (5.07–8.00)  
- Mothers with UC: aIRR for having child with UC 3.71 (3.24–4.25)  
- Mothers with CD: aIRR for having child with CD 6.37 (5.07–8.00)  
- Maternal IBD: For autism spectrum disorders aIRR=0.7 (0.5-1.0)  
Paternal IBD: For autism spectrum disorders aIRR=0.9 (0.6-1.3)  
- Gross motor delay: 6% among exposed versus 3% among unexposed (p=0.11)  
Fine motor delay: 4.4% among exposed versus 8% among unexposed (p=0.19)  
Seizures:
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Follow-up</th>
<th>Maternal IBD</th>
<th>Paternal IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen et al. 2013</td>
<td>Cohort study</td>
<td>All live born children 1979-2009 (nationwide Danish data)</td>
<td>14.9 years</td>
<td>for asthma aIRR=0.97 (0.89-1.06)</td>
<td>for asthma aIRR 0.99 (0.89-1.09)</td>
</tr>
<tr>
<td>Keil et al. 2010</td>
<td>Case Control study</td>
<td>Children born between 1977-2003 diagnosed with autism spectrum disorders and controls (Nationwide Swedish study)</td>
<td>1.227 cases and 30,693 controls</td>
<td>Risk of autism spectrum disorders in the children OR=1.4 (0.8–2.7)</td>
<td>Risk of autism spectrum disorders in the children OR= 1.2 (0.6–2.5)</td>
</tr>
<tr>
<td>Hemminki et al. 2010</td>
<td>Cohort study</td>
<td>Nationwide Swedish data 1964-2004, based on 441,642 patients with autoimmune conditions</td>
<td>25,846 with UC and 18,885 with CD</td>
<td>Mothers and fathers are grouped together.</td>
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</tr>
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<td></td>
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<td>Parents with UC:</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SIR for having child with UC 3.9 (3.5–4.3)</td>
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<td>Parents with CD:</td>
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<td></td>
<td></td>
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<td>SIR for having child with CD 6.0 (5.4–6.7)</td>
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<tr>
<td>Study Reference</td>
<td>Study Type</td>
<td>Study Population</td>
<td>Number of Children</td>
<td>Autism Spectrum Disorder Outcomes</td>
<td>IBD Outcomes</td>
</tr>
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<tr>
<td>Atladottir et al. 2009</td>
<td>Cohort study</td>
<td>All children born 1993 through 2004, in total 689,196 (Nationwide Danish data).</td>
<td>3325</td>
<td>aIRR = 0.76 (0.38-1.33) for child having autism spectrum disorders</td>
<td>Father with CD: aIRR = 0.99 (0.60-1.52) for child having infantile autism</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1089</td>
<td></td>
<td>IBD in mothers of children with infantile autism and in controls:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UC: 2.7% cases, 0.3% controls (p=0.05)</td>
<td>UC: 2.7% cases, 0.3% controls (p=0.05)</td>
</tr>
<tr>
<td>Mouridsen et al. 2007</td>
<td>Case Control study</td>
<td>Children with infantile autism from two areas in Denmark (during 1960-1984).</td>
<td>111</td>
<td>IBD in mothers of children with infantile autism and in controls:</td>
<td>Father with UC: aIRR = 1.05 (0.68-1.53) for child having autism spectrum disorders; aIRR = 1.40 (0.70-2.46) for child having infantile autism</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>105</td>
<td></td>
<td>CD: 0% cases, 0.3% controls (p=1.00).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>330 control mothers, 330 control fathers</td>
<td>IBD in fathers of children with infantile autism and in controls:</td>
<td></td>
</tr>
</tbody>
</table>
Inflammatory bowel disease = IBD  
Ulcerative colitis= UC  
Crohn’s disease = CD  
adjusted standardized incidence ratio = aSIR  
adjusted Incidence rate ratio= aIRR  
Odds ratio = OR  
Adjusted Hazard ratio = aHR

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study Design</th>
<th>Study population</th>
<th>Study details</th>
<th>Offspring outcomes with relative risk estimates (95% confidence interval)</th>
</tr>
</thead>
</table>
| Duricova et al.63 2018 | Cohort study. Anti-TNF exposure in utero (IBD mothers) | Three IBD centers in Czech Republic 2007-2016 | 72 children born to IBD mothers (exposed) and 69 children of non-IBD mothers (unexposed). Follow-up: median 35 months in exposed | Infecions: 
No significant difference in median rate: exposed and unexposed (0.016 vs 0.031, p=0.32) 
Allergy: |
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<td>Chaparro et al.</td>
<td>Cohort study.</td>
<td>Multicenter European study</td>
<td>388 children</td>
<td>In 21 (29.2%) in exposed vs 20 (29.0%) in controls (p = 0.98)</td>
</tr>
<tr>
<td></td>
<td>Anti-TNF exposure in utero (IBD mothers)</td>
<td>453 children of IBD mothers not exposed to anti-TNF in utero.</td>
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<td>Growth and psychomotor development:</td>
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<td></td>
<td>Follow-up: median 47 months in exposed and 68 months unexposed.</td>
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<td>6 (8.3%) in exposed vs 7 (10.1%) in controls had abnormalities (p = 0.71)</td>
</tr>
<tr>
<td>De Meij et al.</td>
<td>Cohort study.</td>
<td>Multicenter study, Netherlands</td>
<td>30 exposed children and 340 unexposed children.</td>
<td>Descriptive data only: No effect on immune function, global medical or psychosocial status</td>
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**Table:**

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</tr>
<tr>
<td>Angelberger et al. [64] 2010</td>
<td>Cohort study</td>
<td>Azathioprine in utero and breastfeeding (IBD mothers)</td>
<td>Outpatient clinic patients in a single center in Vienna (attended May 1999 – January 2007).</td>
<td>15 exposed children exposed to azathioprine <em>in utero</em> and 15 unexposed children. All had mothers with IBD. Median age at time of interview in exposed children 3.3 years exposed, and in unexposed 4.7 years.</td>
</tr>
<tr>
<td>Friedman et al. [41] 2017</td>
<td>Cohort study</td>
<td>Fathers’ use of AZA/6-MP/MTX at the time of conception.</td>
<td>Danish nationwide study (1997 through 2013).</td>
<td>735 children born to fathers who used AZA/6-MP at conception, and 209 children born to fathers who used MTX at conception. Unexposed: 1,056,524 children. Median follow-up time (exposed) 6.7 years and (unexposed) 9.9 years.</td>
</tr>
</tbody>
</table>
Inflammatory bowel disease = IBD
Ulcerative colitis = UC
Crohn’s disease = CD
adjusted Hazard ratio = aHR
azathioprine/6-mercaptopurine = AZA/6-MP
methotrexate = MTX
attention deficit hyperactivity disorder = ADHD
autism spectrum disorders = ASD