American Journal of Gastroenterology 113.3 (2018): 396-403

DOI: https://doi.org/10.1038/ajg.2017.501

Long-term safety of *in utero* exposure to anti-TNFα drugs for the treatment of inflammatory bowel disease: results from the multicenter European TEDDY study

SHORT TITLE: Long-term safety of anti-TNF drugs during pregnancy

AUTHORS: M. Chaparro[1], A. Verreth[2], T. Lobaton[3], E. Gravito-Soares[4], M. Julsgaard[5], E. Savarino[6], F. Magro[7], I. Avni Biron[8], P. Lopez-Serrano[9], M. Casanova[1], M. Gompertz[10], S. Vitor[11], M. Arroyo[12], D. Pugliese[13], Y. Zabana[14], R. Vicente[15], M. Aguas[16], A. Bar-Gil Shitrit[17], A. Gutierrez[18], G. Doherty[19], L. Fernandez-Salazar[20], J. Martínez Cadilla[21], J. Huguet[22], A. O'Toole[23], E. Stasi[24], N. Manceñido Marcos[25], A. Villoria[26], K. Karmiris[27], J. Rahier[28], C. Rodriguez[29], M. Diz-Lois Palomares[30], G. Fiorino[31], J. M. Benitez[32], M. Principi[33], T. Naftali[34], C. Taxonera[35], G. Mantzaris[36], L. Sebkova[37], B. Iade[38], D. Lissner[39], I. Ferrer Bradley[40], A. Lopez-San Roman[41], I. Marin-Jimenez[42], O. Merino[43], M. Sierra[44], M. Van Domselaar[45], F. Caprioli[46], I. Guerra[47], P. Peixe[48], M. Piqueras[49], I. Rodriguez-Lago[50], Y. Ber[51], K. Van Hoeve[2*], P. Torres[3], M. Gravito-Soares[4], D. Rudbeck-Thomsen[5], O. Bartolo[6], A. Peixoto[7], G. Martin[8], A. Armuzzi[13], A. Garre[1], M.G. Donday[1], F.J. Martín de Carpi[52] and J.P. Gisbert[1].

Gastroenterology Units from: [1]Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP) and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain; [2]Department of Gastroenterology and Hepatology, University Hospitals Leuven, KU Leuven, Leuven, Belgium; [2*]Department of Paediatrics, University Hospitals Leuven, KU Leuven, Leuven, Belgium; [3]Hospital Universitari Germans Trias i Pujol and CIBEREHD, Badalona, Spain; [4]Centro Hospitalar e Universitario de Coimbra, Coimbra, Portugal; [5]Aarhus University Hospital, Aarhus, Denmark, [6]University of Padua, Padua, Italy; [7]Centro Hospitalar São João,

Porto, Portugal; [8]Rabin Medical Center, Petaj Tikva, Israel; [9]Hospital Universitario Fundación Alcorcón, Alcorcón, Spain; [10]Hospital Clinic and CIBEREHD, Barcelona, Spain; [11]Hospital de Santa Maria de Lisboa, Lisboa, Portugal; [12]Hospital Clínico de Zaragoza, Zaragoza, Spain; [13]Complesso Integrato Columbus Catholic University, Roma, Italy; [14]Hospital Universitari Mutua de Terrassa and CIBEREHD, Terrassa, Spain; [15]Hospital Universitario Miguel Servet and CIBEREHD, Zaragoza, Spain; [16]Hospital Universitario La Fe, Valencia, Spain; [17]Shaare Zedek Medical Center Jerusalem, Jerusalem, Israel; [18]Hospital General Universitario de Alicante, Alicante, Spain; [19]St. Vincents University Hospital, Dublin, Ireland; [20]Hospital Clinico Universitario de Valladolid, Valladolid, Spain; [21]Hospital Universitario Alvaro Cunqueiro, Vigo, Spain; [22]Hospital General Universitario de Valencia, Valencia, Spain; [23]Beaumont Hospital, Dublin, Ireland; [24]IRCCS Saverio de Bellis, Castellana Grotte, Italy; [25]Hospital Infanta Sofia, Madrid, Spain; [26]Hospital Parc Tauli, Sabadell, Spain; [27]Venizeleio General Hospital, Heraklion, Greece; [28]CHU Dinant Godinne, Dinant, Belgium; [29]Complejo Universitario de Navarra, Pamplona, Spain; [30]Hospital Universitario A Coruña, Coruña, Spain; [31]Humanitas Research Hospital, Milan, Italy; [32]Hospital Reina Sofia, Córdoba, Spain; [33]Azienda Ospedaliera Policlinico de Bari, Bari, Italy; [34]Meir Hospital Kfar saba Tel Aviv University, Tel Aviv, Israel; [35]Hospital Clínico San Carlos, Madrid, Spain; [36]Evangelismos, Ophthalmiatreion Athinon and Polyclinic Hospitals, Atenas, Greece; [37]Azienda Ospedaliera 'Pugliese-Ciaccio", Catanzaro, Italy; [38]Hospital de Clinicas, Montevideo, Uruguay; [39]Universitatsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany; [40]Hospital de Manises, Manises, Spain; [41]Hospital Ramón y Cajal, Madrid, Spain; [42]Hospital General Universitario Gregorio Marañón and CIBEREHD, Madrid, Spain; [43]Hospital Universitario de Cruces, Baracaldo, Spain; [44]Hospital de León, León, Spain; [45]Hospital de Torrejón, Torrejón de Ardoz, Spain; [46]IRCCS Ospedale Ca Granda Policlinico di Milano, Milan, Italy; [47]Hospital Universitario de Fuenlabrada, Fuenlabrada, Spain;

[48]Centro Hospitalar Lisboa Ocidental, Lisboa, Portugal; [49]Consorci Sanitari de Terrasa, Terrasa, Spain; [50]Hospital de Galdakao, Vizcaya, Spain; [51]Hospital San Jorge, Huesca, Spain; [52]Hospital Sant Joan de Deu, Barcelona, Spain.

ABBREVIATIONS: Inflammatory bowel disease (IBD); neonatal Fc receptor (FcRn); 95% confidence interval (95%CI); standard deviation (SD); interquartile range (IQR); anti-tumor necrosis factor (anti-TNF).

KEY WORDS: tumor necrosis factor alpha; infliximab; adalimumab; pregnancy; infant; newborn; infection.

ACKNOWLEDGMENT: The authors thank the Clinical Committee (ClinCom) of the European Crohn and Colitis Organisation (ECCO) and the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) for their support in the study. In addition, the authors wish to thank M Ramas and AG McNicholl for programming the e-CRF in AEG-REDCap and T O'Boyle for the final English language revision funded by MSD.

CORRESPONDENCE

María Chaparro, M.D., Ph.D.

Inflammatory Bowel Disease Unit

Department of Gastroenterology

University Hospital La Princesa

Diego de León, 62, 28006 Madrid, Spain

Tel.: 34-913093911; Fax: 34-914022299

e-mail: mariachs2005@gmail.com

SUMMARY

Background: The long-term safety of exposure to anti-TNF drugs during pregnancy has received little attention.

Aim: We aimed to compare the relative risk of severe infections in children of mothers with inflammatory bowel disease (IBD) who were exposed to anti-TNF drugs *in utero* with that of children who were not exposed to the drugs.

Methods: Retrospective multicentre cohort study. Exposed cohort: children from mothers with IBD receiving anti-TNF medication (with or without thiopurines) at any time during pregnancy or during the three months before conception. Non-exposed cohort: children from mothers with IBD not treated with anti-TNF agents or thiopurines at any time during pregnancy or the three months before conception. The cumulative incidence of severe infections after birth was estimated using Kaplan-Meier curves, which were compared using the log-rank test. Cox-regression analysis was performed to identify potential predictive factors for severe infections in the offspring.

Results: The study population comprised 841 children, of whom 388 (46%) had been exposed to anti-TNF agents. Median follow-up after delivery was 47 months in the exposed group and 68 months in the non-exposed group. Both univariate and multivariate analysis showed the incidence rate of severe infections to be similar in non-exposed and exposed children (1.6 vs. 2.8% per person-year, hazard ratio 1.2 [95% confidence interval 0.8-1.8]). In the multivariate analysis, preterm delivery was the only variable associated with a higher risk of severe infection (2.5% [1.5-4.3]).

Conclusions: *In utero* exposure to anti-TNF drugs does not seem to be associated with increased short-term or long-term risk of severe infections in children.

Introduction

Most patients with inflammatory bowel disease (IBD) are affected during their peak reproductive years, when many female patients affected by Crohn's disease or ulcerative colitis want to have children. Although a diagnosis of IBD does not pose a risk to pregnancy, it has been shown that active disease or a disease flare-up is associated with poor obstetrical outcomes[1-4]. As a result, effective control of disease activity is vital both prior to conception and during pregnancy.

Anti-tumour necrosis factor α (anti-TNFα) drugs have been increasingly used for the treatment of IBD[5]. Therefore, many women wishing to become pregnant may be exposed to these drugs. In this respect, taking anti-TNFα drugs during pregnancy has been considered safe in several registries and observational studies[6]. Nevertheless, their presumed safety is based on short-term data (at delivery or during the first few months postpartum).

The human placenta seems to be impermeable to all antibodies from the maternal immune system except immunoglobulin G (IgG)[7]. Infliximab, adalimumab, and golimumab are IgG1 monoclonal antibodies, whereas certolizumab is a Fab fragment of IgG1 antibody. Materno-fetal transfer of IgG takes place via binding to a specific receptor known as the neonatal Fc or Brambell receptor (FcRn). The FcRn of placental syncytiotrophoblasts is not detected before 14 weeks of gestation[8].

Case series have reported clinically significant infliximab and adalimumab levels in cord blood when these drugs were administered at the end of the second trimester or during the third trimester, although this was not the case for certolizumab pegol[9]. A number of case reports indicate that placental transfer of infliximab leads to prolonged exposure in the neonate. Indeed, serum levels in neonates are often higher than those in maternal serum and remain detectable up to six months after birth, probably as a result of the immaturity of

the reticuloendothelial system, which leads to slow antibody clearance[10]. However, the effects of these high drug levels on the developing immune system are unknown.

The inital results of two series showed that children with high drug levels did not seem to have an increased risk of infection in their first year of life and that they had a normal response to inactivated vaccines[1, 11]. In newborns exposed to anti-TNFα *in utero*, high levels of the drug are present during a period that is crucial for the development of the immune system.

In summary, anti-TNFα treatment during pregnancy seems to be relatively safe in the short-term. However, the long-term effects of intrauterine exposure to anti-TNFα drugs remain uncertain. Therefore, the primary aim of the present study was to compare the relative risk of severe infections in children from mothers with IBD who have been exposed to anti-TNFα drugs *in utero* with that of children who were not exposed. The secondary aims were to compare the prevalence of malformations in children exposed to anti-TNFα drugs *in utero* with that of children who were not exposed, to evaluate the relative risk of developing neoplasm in children exposed to anti-TNFα drugs, and to ascertain the relative risk of complications in children exposed to anti-TNFα drugs.

METHODS

We designed a retrospective multicenter cohort study of children born to women diagnosed with IBD and treated with anti-TNFα drugs during pregnancy or the three months before conception. In order to identify the long-term effects of these drugs on offspring, we also included a non-exposed cohort with children born to women with IBD who did not receive anti-TNFα drugs during their pregnancies. The principal variable was the risk of severe infection, defined as an infection that led the child to be admitted to hospital. Children were followed from birth to the date of inclusion, when mothers were contacted (2014 in most cases). In order to minimize heterogeneity in the management of IBD, inclusion was limited to pregnancies occurring after 1999, when infliximab was approved for IBD in Europe. Practitioners specialized in IBD identified women from their practice who received or did not receive anti-TNFα drugs for IBD during their pregnancy. In order to avoid selection bias, clinicians were asked to systematically review their databases in order to identify patients who met the inclusion criteria. In addition, clinicians were asked to contact women whose reproductive age (15 to 50 years) was within the study timeframe. The study was approved by the ethics committees of each participating center and by the Spanish Agency of Medicines and Medical Devices.

Study population

- Exposed cohort: Children from mothers treated with anti-TNFα drugs either in monotherapy or in combination with thiopurines at any time during pregnancy or during the three months before conception.
- Non-exposed cohort: Children from mothers not treated with anti-TNFα drugs or thiopurines at any time during pregnancy or during the three months before conception.

Data collection

Women who had been pregnant within the study timeframe at each participating centre were contacted to obtain information about the development of their children. Data were obtained from the medical records at the participating centre and medical reports on the delivery. In addition, the mothers provided information of the children's admissions to hospital. In the case of missing data, the mothers were asked to obtain them. Finally, cases with relevant missing data were ruled out after contacting the investigator. The variables included in the database were IBD type, age at diagnosis of IBD, age at conception, comorbidities, smoking habit and alcohol consumption during pregnancy, surgical interventions due to IBD, folic acid supplementation during pregnancy and conception, medical treatment during conception, pregnancy and breastfeeding (including all drugs, whether associated or not with IBD), complications during pregnancy and delivery, newborn complications, breastfeeding, infant allergies, vaccinations, and infant complications until the end of follow-up (eg, severe infections and neoplasms). The data collected on severe infections were type of infection, date of infection, length of stay, and need for admission to the intensive care unit.

Study data were collected and managed using an electronic data capture tool (Research Electronic Data Capture [REDCap]), which is hosted at Asociación Española de Gastroenterología (AEG; www.aegastro.es)[12], a non-profit scientific and medical society focusing on gastroenterology. AEG provided this service free of charge, with the sole aim of promoting independent investigator-driven research. REDCap is a secure, web-based application designed to support data capture for research studies that provides the following: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data

downloads to common statistical packages; and 4) procedures for importing data from external sources.

Definitions

- Complications: Any complication recorded during pregnancy or delivery or in the newborn.
- Complication during pregnancy: At least one of the following outcomes during pregnancy: growth retardation, infection, eclampsia, placenta previa, chorioamnionitis, or abruptio placenta.
- Complication during delivery: At least one complication during delivery, such as instrumental delivery, caesarean section, or preterm delivery.
- Newborn complications: At least one complication in the newborn, such as congenital malformations, admission to the intensive care unit, low birth weight, or low Apgar score.
- Severe infection: An infection that led the child to be admitted to hospital at any time during follow-up.
- Preterm delivery: Delivery before week 37 of gestation[3, 4].
- Low birth weight: <2,500 mg[3, 4].
- IBD activity: IBD activity was assessed before conception and during each trimester of gestation based on the Harvey-Bradshaw index for Crohn's disease and the Partial Mayo Score for ulcerative colitis. The medical records were consulted to obtain the variables needed to calculate the score.
- Low Apgar score: Apgar scores lower than 7 were considered low, and scores of 7 or higher were considered normal at ten minutes after birth[13]

Statistical analysis

Quantitative variables were expressed as the mean and standard deviation (SD) or the median and interquartile range (IQR), depending on whether they were normally distributed or not. Categorical variables were expressed as percentages and 95% confidence intervals (CI). Means were compared using the *t* test for independent samples or the Mann-Whitney test (according to the distribution of data). Categorical variables were compared using the χ^2 test and Fisher exact test or the Wilcoxon rank-sum test according to the distribution of data. Statistical significance was set at $p<0.05$ for the overall comparison of the cohorts (non-exposed and exposed to anti-TNFα drugs).

The cumulative incidence of severe infection after birth was estimated using Kaplan-Meier curves, which were compared using the log-rank test. Cox regression analysis was performed to identify independent predictors of severe infection. In the Cox regression model, the dependent variable was the presence of severe infection, and the independent variables were those which were considered clinically relevant (eg, type of IBD, maternal age at conception, consumption of toxic substances during pregnancy, IBD activity at the moment of conception, disease activity during pregnancy, low birth weight, prematurity, and exposure to anti-TNFα drugs) and those which reached statistical significance in the univariate analysis.

RESULTS

A total of 841 children were included. Of these, 388 (46%) had been exposed to anti-TNFα drugs *in utero* and 453 (54%) had not been exposed. The demographic characteristics of the children's mothers are summarized in table 1. Of note, the proportion of Crohn's disease, previous surgery, and smoking habit was higher among mothers from the exposed cohort. Of the children exposed to anti-TNFα drugs, 57.4% had been exposed to infliximab, 42.3% to adalimumab, and 0.3% to certolizumab pegol (table 2). Ninety-nine (25%) had also been exposed to thiopurines.

The overall proportion of complications during pregnancy was similar in the exposed and non-exposed cohorts (14.9% vs. 17.7%, p=0.29). However, the proportion of infections in mothers treated with anti-TNFα drugs during gestation was higher in the exposed cohort (4.1% vs. 0.9%, p=0.002). Other complications, such as premature rupture of membranes, chorioamnionitis, placenta previa, eclampsia, and fetal growth retardation, were equally distributed in both groups (table 3).

On the other hand, the proportion of complications during delivery was significantly higher in the exposed cohort (57.5% vs. 43.5%, p<0.01). As for type of complications, the proportion of caesarean sections was significantly higher in the exposed group (44% vs. 32%, p<0.01). When caesarean section was not considered a complication (ie, planned and emergency), the proportion of delivery complications was still higher in the exposed group (20.4% vs. 14.6%, p=0.02). The distribution of other complications, such as instrumental delivery or preterm delivery, was similar between both groups (table 3).

Finally, the proportion of children with complications after birth was significantly higher in the exposed cohort (19% vs. 10.5%, p<0.01). Similarly, the proportion of children admitted to the intensive care unit was significantly higher in the exposed cohort (7% vs. 3.1%,

p<0.01), as was the prevalence of children with low birth weight (9.8% vs. 5%, p<0.01). Other complications, such as congenital malformation or low Apgar score, were equally distributed between the groups.

Severe infections in the offspring during follow-up

A total of 90 children developed severe infection during follow-up, 46 (12%) in the exposed cohort and 44 (9.7%) in the non-exposed cohort (p=0.3), although all of the infections resolved. In addition, three (3%) of the 90 children developed two severe infections during follow-up, and two children (2%) developed three severe infections, although all of the infections resolved. Median follow-up time in the overall group was 68 months (range, 13 to 216 moths): 68 months (range, 13 to 216 months) in the non-exposed group, and 47 months (range, 9 to 202 months) in the exposed cohort. The incidence rate of infection was similar between both groups (figure 1): 2.8% per person-year in the exposed cohort and 1.6% per person-year in the non-exposed cohort (p=0.2).

As expected, the most prevalent infections were respiratory infections, followed by gastrointestinal infections and urinary infections (table 4). With respect to time of onset of the infection, median age at diagnosis of severe infection was 8.2 months in the exposed group (range, 0 to 80 months) and 7.5 months (range, 0 to 72 months) in the non-exposed group (p>0.05). In particular, 66% of the severe infections in the exposed cohort and 64% of those in the non-exposed cohort occurred within the first year of life.

Mean length of stay due to severe infection was 7.5 days in the exposed group and 6.3 days in the non-exposed group (p>0.05). In addition, the need for admission to the intensive care unit owing to severe infection was similar in both cohorts (p>0.05). Furthermore, the length of admission in the intensive care unit did not differ between the groups (p>0.05).

In the univariate analysis, only preterm delivery was associated with a higher risk of severe infection after birth (p<0.001) (figure 2). No other variables (eg, intrauterine exposure to thiopurines, active disease during pregnancy, maternal smoking, or exposure to anti-TNFα drugs [including exposure during the third trimester in comparison with non-exposure and, within the exposed cohort, exposure during the third trimester in comparison with children not exposed during the third trimester]) were associated with a higher risk of severe infection. The association remained significant in the multivariate analysis (table 5). After adjustment for low-birth weight, only preterm delivery was associated with a higher risk of infection (hazard ratio, 2.5; 95%CI, 1.5-4.3).

Severe infection in children exposed to both thiopurines and anti-TNF drugs

Ninety-nine children in the exposed group (25%) had received combination therapy with anti-TNF and thiopurines *in utero*. Eleven children (11%) in the combination group and 35 (12%) in the anti-TNFα monotherapy group developed a severe infection. The prevalence of severe infections was similar among children exposed to anti-TNFα in monotherapy and in those whose therapy was combined with thiopurines (12% vs. 11%, p>0.05). Moreover, the cumulative incidence of severe infection was similar in both groups.

Other outcomes during follow-up

No children developed neoplasms during follow-up. The proportion of children who were not vaccinated according to local guidelines was significantly higher in the exposed cohort (6% vs. 1.3%, p<0.01). A total of 41 children in the exposed cohort (10.6%) developed allergies during follow-up, as did 36 (7.9%) in the non-exposed cohort (p>0.05).

DISCUSSION

The results of the present study show that exposure to anti-TNFα drugs *in utero* does not increase the risk of severe infections in children born to mothers with IBD. To our knowledge, this is the largest cohort of children exposed *in utero* to anti-TNFα drugs (approximately 400 children) and with the longest follow-up (mean of four years). We found that the incidence rate of severe infection was 2.8% per person-year in the exposed cohort and 1.6% per person-year in the non-exposed cohort. Data about the incidence rate of severe infection in children in the general population are scarce. An epidemiological study performed in the Valencia region of eastern Spain estimated that the incidence rate of admission due to infections in a pediatric population was 1.7% per patient-year, which was similar to the figure we found in the non-exposed cohort[14].

To date, most studies on the safety of anti-TNFα drugs during pregnancy have focused on gestation and delivery or, in some cases, on the immediate postpartum[6]. Data from those studies support the safety of anti-TNFα drugs, at least in the short term. However, caution about the use of these drugs during pregnancy is advised owing to the lack of data on the long-term impact in children exposed to anti-TNFα drugs.

Many studies have demonstrated the presence of detectable anti-TNFα drugs in the serum of infants born to mothers receiving these agents during pregnancy[9, 15, 16] In fact, median cord blood drug concentration seems to be higher than maternal serum drug concentration. In addition, an inverse correlation has been reported between the time since the most recent drug exposure and both cord blood and maternal blood concentration[9, 15]. Immaturity of the reticuloendothelial system leading to slow antibody clearance is probably responsible for this effect[15, 17].

TNFα plays an important role in embryonic and fetal development. Increased embryonic death and structural defects have been detected in TNFα knockout mice compared with the wild type[18]. However, blockade of TNFα by antagonists, as opposed to gene knockout, may have different effects on the developing fetus. The role of TNFα in human pregnancy is not fully understood. During fetal development, the TNFα superfamily members lymphotoxin-α and -β play an important role in the development and organization of secondary lymphoid tissues[19].

It is well known that anti-TNFα agents are unlikely to cross the placenta in the first trimester, although they do so very efficiently in the late second and third trimesters[20]. This may protect the infant from exposure during the crucial period of organogenesis in the first trimester. However, placental transfer in the third trimester means that anti-TNFα agents can be present in the infant for several months after delivery, thus raising concerns about immune system development and the consequent risk of infections.

In this respect, preliminary results from the PIANO study were presented at Digestive Diseases Week in 2012[21]. In this prospective cohort study performed at 30 IBD centers in the USA, patients were classified according to exposure between conception and delivery. Women were contacted during each trimester, at delivery, and at 4, 9, and 12 months after delivery. At the time of the sub-analysis, 102 women had been treated with anti-TNFα drugs during pregnancy, and 59 women had received both thiopurines and anti-TNFα agents. The authors reported that the use of thiopurines and anti-TNFα agents was not associated with an increased rate of complications, such as spontaneous abortion, congenital anomalies, preterm birth, intrauterine growth retardation, and caesarean section. However, a significant increase in the frequency of infections was recorded in infants aged 9-12 months in the combination therapy group (mothers receiving both thiopurines and anti-TNFα agents) compared with the unexposed group. As the anti-TNFα drug is generally no longer

detectable in infants aged 9-12 months, the authors stated that this finding might suggest dysfunctional immune development and thus merits further investigation.

In our cohort study, children in the exposed cohort were born from mothers with more aggressive IBD: more had Crohn's disease, the prevalence of previous surgery due to IBD was also higher, and more intensive therapy was necessary to control disease activity (such as anti-TNFα with or without thiopurines). Nevertheless, the incidence rate of severe infection was similar in the exposed and non-exposed cohorts. Only preterm-delivery (adjusted for low-birth weight) was significantly associated with a higher risk of infection. However, neither treatment with anti-TNFα drugs nor combined therapy with thiopurines was significantly associated with a higher risk of severe infection. Of note, given that only live births were included in our study, the risk of complications during pregnancy and delivery could not be assessed.

We were unable to find any difference between the exposed and non-exposed groups with respect to severity of infection. In this respect, the length of hospital stay and the proportion of infants admitted to the intensive care unit with severe infection were similar in both cohorts.

Julsgaard et al recently published a study investigating the impact of anti-TNFα concentration on infant development and the risk of infections during the first year of life after *in utero* exposure[9]. Data were obtained from 80 mother-baby pairs for the long-term follow-up assessment. In this study, 4 children (5%) developed bacterial infections during follow-up (12 months). In addition, 16 infants developed viral infections, all of which had a benign course. The median anti-TNFα concentration at birth was not higher among infants who contracted an infection during their first year of life than in those who were not infected. In the same way, continuing maternal anti-TNFα treatment after week 30 did not increase the risk of infection in comparison with discontinuation before week 30.

In line with the above-mentioned preliminary analysis of the PIANO cohort, Julsgaard et al found a greater risk of infections during the first year of life in the infants of mothers who received combination therapy (anti-TNFα and thiopurines) during pregnancy (relative risk 2.7, 95%CI 1.5-6.78) than in those exposed only to anti-TNFα drugs. However, other studies have not shown a higher risk of infection among children exposed to combination therapy *in utero* than among those exposed only to anti-TNFα drugs.

A sub-analysis in the exposed cohort to compare the outcomes of children exposed to anti-TNFα in monotherapy with those of children exposed to combination therapy revealed no difference in the incidence of severe infection. However, our primary endpoint was severe infection, and our study was not sufficiently powered to analyze other types of infection.

Our findings are subject to a series of limitations, mainly those arising from its retrospective design. To avoid selection bias, clinicians were asked to systematically review their databases in order to identify all patients who met the inclusion criteria. Therefore, missed patients, if any, could have been from both the exposed and the non-exposed groups. In addition, women who had been pregnant within the study timeframe were contacted after identification to obtain information about the development of their children. Therefore, the doctor was not aware of the onset of severe infections in children before contacting the mothers. In this respect, we think that the risk of bias is low, as is its impact on the interpretation of the results. On the other hand, data on the infection, such as the identification of the agent causing the disease, were not available. Second, as we decided to focus on severe infection (infection causing hospital admission) to avoid recall bias, we had no information about mild infections. Third, developmental milestones could not be evaluated, although several studies did not find impaired development in exposed children, and, in any case, this was not an objective of our study[9, 23]. In addition, information about the

proportion of children in kindergarten was not available; however, we would not expect this percentage to differ between the groups. Finally, since samples to assess the concentration of anti-TNFα serum and cord blood levels were not available, the relationship between the risk of severe infection and drug levels could not be assessed.

Our study also has a series of strengths. It is the largest study to date to assess the long-term impact of anti-TNFα drugs on the offspring of mothers with IBD. It also has the longest follow-up period. Despite its retrospective design, it is obvious that a prospective study with a sufficiently large sample would take many years to provide long-term information about the impact of anti-TNFα drugs on the risk of infections in children. In addition, the risk of recall bias of the principal variable (severe infection) should be low, as parents can easily remember whether their children have been admitted to hospital. Furthermore, relevant information such as complications of pregnancy or delivery and details about admissions due to infection could easily be found in the medical reports at discharge.

In conclusion, our large observational study found that exposure to anti-TNFα drugs during pregnancy in mothers with IBD did not increase the long-term risk of severe infection in offspring. Preterm birth increases the risk of severe infection in infants born to women with IBD. The risk of severe infection does not seem to be higher in children exposed to both anti-TNFα and thiopurines, although this association should be investigated further, as our study was not sufficiently powered to evaluate the issue.

REFERENCES

1. Mahadevan U, Kane S, Church JA. The effect of maternal peripartum infliximab use on neonatal immune response. Gastroenterology 2008; 134: A69.

2. Gisbert JP. Safety of immunomodulators and biologics for the treatment of inflammatory bowel disease during pregnancy and breast-feeding. Inflamm Bowel Dis 2010; 16: 881-895.

3. van der Woude CJ, Ardizzone S, Bengtson MB, Fiorino G, Fraser G, Katsanos K, et al. The second European evidenced-based consensus on reproduction and pregnancy in inflammatory bowel disease. J Crohns Colitis 2015; 9: 107-124.

4. Nguyen GC, Seow CH, Maxwell C, Huang V, Leung Y, Jones J, et al. The Toronto Consensus Statements for the Management of Inflammatory Bowel Disease in Pregnancy. Gastroenterology 2016; 150: 734-757 e731.

5. Burisch J, Pedersen N, Cukovic-Cavka S, Turk N, Kaimakliotis I, Duricova D, et al. Initial disease course and treatment in an inflammatory bowel disease inception cohort in Europe: the ECCO-EpiCom cohort. Inflamm Bowel Dis 2014; 20: 36-46.

6. Gisbert JP, Chaparro M. Safety of anti-TNF agents during pregnancy and breastfeeding in women with inflammatory bowel disease. Am J Gastroenterol 2013; 108: 1426-1438.

7. Mix E, Goertsches R, Zett UK. Immunoglobulins--basic considerations. J Neurol 2006; 253 Suppl 5: V9-17.

8. Israel EJ, Simister N, Freiberg E, Caplan A, Walker WA. Immunoglobulin G binding sites on the human foetal intestine: a possible mechanism for the passive transfer of immunity from mother to infant. Immunology 1993; 79: 77-81.

9. Julsgaard M, Christensen LA, Gibson PR, Gearry RB, Fallingborg J, Hvas CL, et al. Concentrations of Adalimumab and Infliximab in Mothers and Newborns, and Effects on Infection. Gastroenterology 2016; 151: 110-119.

10. Vermeire S, Carbonnel F, Coulie PG, Geenen V, Hazes JM, Masson PL, et al. Management of inflammatory bowel disease in pregnancy. J Crohns Colitis 2012; 6: 811-823.

11. Zelinkova Z, de Haar C, de Ridder L, Pierik MJ, Kuipers EJ, Peppelenbosch MP, et al. High intra-uterine exposure to infliximab following maternal anti-TNF treatment during pregnancy. Aliment Pharmacol Ther 2011; 33: 1053-1058.

12. Harris PA, Taylor T, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42: 377-381.

13. Boyd HA, Basit S, Harpsoe MC, Wohlfahrt J, Jess T. Inflammatory Bowel Disease and Risk of Adverse Pregnancy Outcomes. PLoS One 2015; 10: e0129567.
14. Guerrero Espejo A, Tomas Dols S. [Hospital admissions for infectious diseases: 1999-2003 incidence in one health district in the autonomous community of Valencia, Spain]. Rev Esp Salud Publica 2007; 81: 411-420.
15. Mahadevan U, Wolf DC, Dubinsky M, Cortot A, Lee SD, Siegel CA, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2013; 11: 286-292; quiz e224.
16. de Lima A, Zelinkova Z, van der Ent C, Steegers EA, van der Woude CJ. Tailored anti-TNF therapy during pregnancy in patients with IBD: maternal and fetal safety. Gut 2016; 65: 1261-1268.
17. Steenholdt C, Al-Khalaf M, Ainsworth MA, Brynskov J. Therapeutic infliximab drug level in a child born to a woman with ulcerative colitis treated until gestation week 31. J Crohns Colitis 2012; 6: 358-361.
18. Wen L, Shinton SA, Hardy RR, Hayakawa K. Association of B-1 B cells with follicular dendritic cells in spleen. J Immunol 2005; 174: 6918-6926.
19. Arsenescu R, Arsenescu V, de Villiers WJ. TNF-alpha and the development of the neonatal immune system: implications for inhibitor use in pregnancy. Am J Gastroenterol 2011; 106: 559-562.
20. Chaparro M, Gisbert JP. Transplacental transfer of immunosuppressants and biologics used for the treatment of inflammatory bowel disease. Curr Pharm Biotechnol 2011; 12: 765-773.
21. Mahadevan U, Martin C, Sandler R, Kane S, Dubinsky M, Lewis J, et al. PIANO: A 1000 patients prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy. Gastroenterology 2012; 138: S149.
22. Lin K, Martin C, Dassopoulos T, Esposti S, Wolf D, Esposti S, et al. Pregnancy Outcomes Amongst Mothers With Inflammatory Bowel Disease Exposed to Systemic Corticosteroids: Results of the PIANO Registry. Gastroenterology 2014; 146: S1.
23. Mahadevan U, Martin C, Chambers C, Kane S, Dubinsky M, Sandborn W, et al. Achievement of Developmental Milestones Among Offspring of Women With Inflammatory Bowel Disease: The PIANO Registry. Gastroenterology 2014; 146: S1.

Table 1. Demographic characteristics of the mothers of children included in the study.

	Exposed cohort (N= 388)	Non-exposed cohort (N=453)	p
Median age (years)	31	32.5	0.001
Crohn's disease (%)	75	42	0.001
Smoking habit (%)	10.2	7	0.006
Previous intestinal resection due to IBD (%)	35	18	0.001
Active disease TM1 (%)	28	26	0,7
Active disease TM2 (%)	33	26.6	0.2
Active disease TM3 (%)	28	26.4	0.7
Breastfeeding (%)	57	78	0.005
Median duration of breastfeeding (months)	5.6	8.1	0.001

IBD, inflammatory bowel disease; TM, trimester.

Table 2. Exposure to drugs during pregnancy.

Not exposed to anti-TNFα drugs, N (%)	453 (54%)
Exposed to anti-TNFα drugs, N (%)	388 (46%)
Drug	
Infliximab, N (%)	223 (57.4%)
Adalimumab, N (%)	164 (42.3%)
Certolizumab pegol, N (%)	1 (0.3%)
Time of exposure	
First trimester, N (%)	353 (91%)
Second trimester, N (%)	345 (89%)
Third trimester, N (%)	148 (38%)
Concomitant treatment with thiopurines	99 (25.5%)
First trimester, N (%)	94 (24.2%)
Second trimester, N (%)	92 (23.7%)
Third trimester, N (%)	86 (22.2%)

N, number of children.

Table 3. Prevalence of complications during pregnancy and delivery and complications affecting newborn's complications.

	Exposed cohort N=388	Non-exposed cohort N=453	p
Complications during pregnancy (%)	14.9	17.7	0.29
Growth retardation	3.4	2.9	0.68
Infection	4.1	0.9	0.002
Eclampsia	1.3	0.9	0.5
Placenta previa	0.5	0.4	0.8
Chorioamnionitis	0.3	0.4	0.6
Abruptio placenta	5.2	6	0.61
Delivery-related complications (%)*	57	43	0.001
Instrumental delivery	11.6	7.7	0.05
Caesarean section	43.8	32	0.001
Preterm delivery	10.6	7.3	0.09
Newborn complications (%)	24.5	16	0.002
Congenital malformations	5.4	2.6	0.06
Intensive care unit admission	7	3.1	0.009
Low-birth weight	10.6	6.8	0.05
Low Apgar score	14.7	11.5	0.16

* Delivery-related complications excluding caesarean section: 20.4% exposed cohort vs. 14.6% non-exposed cohort (p=0.02)

514 Table 4. Types of severe infection by cohort.
515

	Exposed cohort	Non-exposed cohort
None, N (%)	342 (88.1)	409 (90.3)
Respiratory infection, N (%)	22 (5.7)	24 (5.3)
Urinary infection, N (%)	7 (1.8)	3 (0.7)
Gastrointestinal infection, N (%)	6 (1.5)	6 (1.3)
Unknown location, N (%)	2 (0.5)	4 (0.9)
Appendicitis, N (%)	1 (0.3)	0 (0)
Arthritis, N (%)	1 (0.3)	0 (0)
Coxsackievirus, N (%)	1 (0.3)	0 (0)
Mastoiditis, N (%)	1 (0.3)	0 (0)
Pertussis, N (%)	1 (0.3)	0 (0)
Sialadenitis, N (%)	1 (0.3)	0 (0)
Skin infection, N (%)	1 (0.3)	3 (0.7)
Stomatitis, N (%)	1 (0.3)	0 (0)
Tonsillitis, N (%)	1 (0.3)	1 (0.2)
Meningitis, N (%)	0 (0)	1 (0.2)
Mononucleosis, N (%)	0 (0)	1 (0.2)
Sinusitis, N (%)	0 (0)	1 (0.2)

516
517
518 N, number of children.
519
520

Table 5. Factors associated with the risk of severe infection in offspring during follow-up.

	Hazard ratio	95% Confidence interval	p
Exposed (vs. non-exposed)	1.2	0.8-1.8	0.3
Preterm delivery	2.9	1.5-5.5	0.001
Low birth weight	0.7	0.3-1.6	0.4

Figure 1. Survival curves for the cumulative incidence of severe infection by exposure to anti-TNFα during pregnancy.

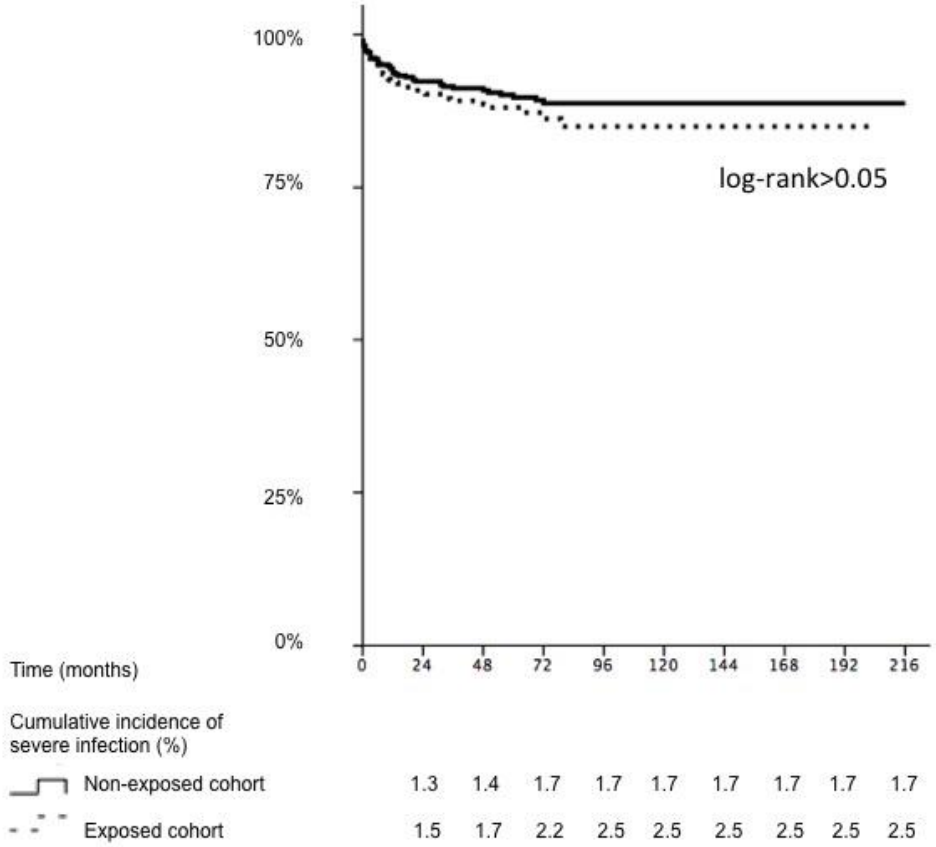

Figure 2. Survival curves for the cumulative incidence of severe infections by preterm-delivery.