Received: 31 March 2020 | First decision: 26 April 2020 | Accepted: 26 June 2020

DOI: 10.1111/apt.15971

AP&T Alimentary Pharmacology & Therapeutics WILEY

Paediatric infections in the first 3 years of life after maternal anti-TNF treatment during pregnancy

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Funding information
The study was developed from post-approval studies that the US Food and Drug Administration and the European Medicines Agency requested as post-marketing commitments from pharmaceutical companies that manufacture anti-TNF agents; Janssen, manufacturer of Remicade® (infliximab) and Pfizer, manufacturer of Enbrel® (etanercept). The study design and the collection, analysis and interpretation of the data were conducted by the researchers who also wrote the report and made an independent decision to submit the article for publication.

Summary

Background: Most anti-tumour necrosis factor (anti-TNF) agents are transferred across the placenta and may increase paediatric susceptibility to infections.

Aims: To assess the risk of paediatric infections after maternal anti-TNF treatment.

Methods: Population-based cohort study in Denmark, Finland and Sweden 2006-2013 in which 1027 children born to women with rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis or inflammatory bowel disease, treated with anti-TNF, and 9346 children to women with non-biologic systemic treatment, were compared to 1 617 886 children of the general population. Children were followed for 3 years.

Results: Adjusted by maternal age, parity, smoking, body mass index, country and calendar year, the incidence rate ratios with 95% confidence interval (CI) for hospital admissions for infection in the first year were 1.43 (1.23-1.67) for anti-TNF and 1.14 (1.07-1.21) for non-biologic systemic treatment, and 1.29 (1.11-1.50) and 1.09 (1.02-1.15), respectively, when additionally adjusting for adverse birth outcomes. There was a slight increase in antibiotic prescriptions in the second year for anti-TNF, 1.19 (1.11-1.29), and for non-biologic systemic treatment, 1.10 (1.07-1.13). There was no difference among anti-TNF agents, treatment in the third trimester, or between mono/combination therapy with non-biologic systemic treatment.

Conclusions: Both anti-TNF and non-biologic systemic treatment were associated with an increased risk of paediatric infections. However, reassuringly, the increased risks were present regardless of treatment in the third trimester, or with combination treatment, and were not persistent during the first 3 years of life. Our findings may indicate a true risk, but could also be due to unadjusted confounding by disease severity and healthcare-seeking behaviour. This may in turn shift the risk-benefit equation towards continuation of treatment even in the third trimester.

The Handling Editor for this article was Professor Richard Gearry, and it was accepted for publication after full peer-review.
The complete list of authors' affiliation list are listed in Appendix 1.

1 | INTRODUCTION

The safety of treatment during pregnancy is a concern for women with rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis and inflammatory bowel disease (IBD), as their onset often coincides with the reproductive age.[1-5] Furthermore, active disease during pregnancy is associated with adverse birth outcomes.[6-8] Treatment directed at tumour necrosis factor (TNF), a key cytokine in the inflammatory processes of these diseases, suppresses inflammation but also increases the risk of infection.[9-12] There is limited knowledge on the child's risk of infections after maternal treatment with infliximab, adalimumab, etanercept, golimumab and certolizumab-pegol.

Infliximab, adalimumab and golimumab are full monoclonal antibodies that cross the placenta by active transport starting in the first trimester, but to a significant degree from the late second trimester and increasingly beyond.[13] Etanercept consists of an antibody Fc fragment and has some transplacental transport.[14] Certolizumab-pegol is a PEGylated antibody Fab' fragment which lacks the Fc fragment, and therefore has very limited transplacental transport.[15] Accordingly, infliximab and adalimumab have been detected in infant circulation and may remain detectable up to 6-12 months,[16,17] while certolizumab-pegol is not transferred to any large extent.[15] Follow-up studies of anti-TNF transfer to the foetus have been conflicting, some presenting an increased infection frequency after exposure to combination therapy with anti-TNF and thiopurines,[16,18] and others reporting no increased frequency.[9,19-21]

In this three-country population-based cohort, we studied the risks of hospital admissions for infection and antibiotic prescriptions in children born to women with anti-TNF treatment during pregnancy compared to i) women with the same diseases, but no anti-TNF treatment, and ii) women without disease in the general population.

2 | MATERIALS AND METHODS

We conducted a population-based study in Denmark (2006-2013), Finland (2006-2012) and Sweden (July 2006-2013) obtaining data from the national medical birth registers, patient registers and prescribed drug registers.[22-26] In these countries, healthcare is accessible to all free of charge and reporting to the national registers is mandatory, resulting in virtually complete coverage and we included all pregnancies. In Finland and Sweden, we also included treatment data from the disease-specific registers. A unique personal identification number assigned at birth or upon immigration enables the linkage of individual data between registers in each country.

The medical birth registers prospectively record information on pregnancy, delivery and the neonatal period.[22] Start of pregnancy and gestational age were based primarily on the routine early pregnancy ultrasound, offered to all pregnant women.

2.1 | Anti-TNF and nonbiologic systemic treatment

Exposure to anti-TNF was defined by filled prescriptions for etanercept, infliximab, adalimumab, certolizumab-pegol or golimumab in the national registers of prescribed drugs, by Anatomical Therapeutic Chemical Classification System (ATC) codes.[23] People can get reimbursed an amount of medication equivalent to 3 months of treatment at a time. Therefore, the period of exposure, from 90 days before first day of last menstrual period until delivery, was defined by days' supply of the medication based on patient's previous prescription fill interval, defined daily doses or the median treatment interval for each anti-TNF agents. In Denmark, anti-TNF treatment was also identified from visits recorded in the patient register covering all Danish hospitals using a specific treatment code.[25] In Finland, information was also obtained from the register for biologic treatment (ROB-FIN) and in Sweden, additional information on anti-TNF treatment was obtained from the ARTIS and PsoReg registers.[27,28]

Nonbiologic systemic treatment in women with disease was defined by the date of filled prescriptions within 90 days before first day of last menstrual period and until delivery according to a list of medications with immunomodulatory effects (Table S1).

2.2 | Inflammatory diseases

We obtained information on chronic inflammatory diseases as codes according to the International Classification of Diseases version 10 (ICD-10) recorded before or during pregnancy in the patient registers, disease-specific registers and the medical birth registers (Table S2). The patient registers record inpatient and outpatient visits to medical specialists, eg gastroenterologists, dermatologists and rheumatologists. For patients diagnosed with more than one chronic inflammatory disease, the most recent diagnosis was used. We refer to the disease types as IBD (ulcerative colitis and Crohn's disease) and ARTPSO (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and psoriasis).

2.3 | Paediatric infections

For the children, we identified primary and secondary diagnoses of infections in hospital admissions (list in Table S3) and filled prescriptions of antibiotics, in the first 3 years of life in the patient registers and the prescribed drug registers. In Finland, children were followed to 1 year of age.

2.4 | Covariates

Covariates included country, maternal diagnosis, maternal age, parity, smoking and body mass index. We identified the children born preterm (<37 weeks), born by caesarean section, of low birth weight

(<2500 g) and small for gestational age (weight below 2 standard deviations for the gestational age).

2.5 | Statistical analysis

We assessed hospital admissions for infection and antibiotic prescriptions in children born to (a) women with anti-TNF, (b) women with nonbiologic systemic treatment and (c) women of the general population. In the main analyses, the general population was the reference. To take confounding by indication into account, anti-TNF treatment was in additional analyses also compared to nonbiologic systemic treatment. Children were censored after their first event in each quarter, ie 3-month period, but could then go on to contribute with another event in the next quarter unless censored by loss to follow-up. We analysed recurrent event data with Poisson regression applying the generalised estimating equations model to account for correlation between the four repeated events for each year of follow-up. We computed incidence rate ratios (IRRs) and corresponding 95% confidence intervals (CIs) for hospital admissions for infection and antibiotic prescriptions, comparing rates for children born to women with chronic inflammatory disease with anti-TNF treatment and women with nonbiologic systemic treatment to women of the general population. In order to estimate the total effect of exposures (ie including effects mediated through adverse birth outcomes) we adjusted for maternal age (≤19 years, 20-24 years, 25-29 years, 30-34 years and ≥35 years), parity (primiparous/multiparous), smoking (yes/no), body mass index in kg/m^2 (≤19.9, 20.0-24.9, 25.0-29.9 and ≥30), country of birth (Denmark/Finland/Sweden), separate calendar year effects for each country and, for comparisons with nonbiologic systemic treatment as the reference, type of chronic inflammatory diagnosis (Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and psoriasis) (IRR1). The reason for allowing different calendar year effects for each country was that the number of patients treated with anti-TNF increased with calendar time at the same time as we observed country-specific decreasing trends of prescribed antibiotics. When estimating the direct effect of the exposure we additionally adjusted analyses by preterm birth, caesarean section, low birth weight and small for gestational age (IRR 2). Hospital admissions for infection and prescribed antibiotics according to the age of the child were presented in figures and calculated by estimating the adjusted IRRs per quarter of age and then multiplying these estimates with the average incidences over the study period in the general population comparator in Sweden and Denmark, for which data were available for all 3 years. To estimate the impact of disease and treatment interaction, we analysed the rates of infections by disease type; IBD or ARTPSO. We also analysed adalimumab, etanercept and infliximab separately.

We assessed IRRs of anti-TNF in combination with nonbiologic systemic treatment and anti-TNF monotherapy compared with the general population. We also estimated the risks in patients treated with anti-TNF in the third trimester (after 26 gestational weeks), with or without earlier treatment, and in patients treated before the third trimester only.

Analyses assessing IRR's for nonbiologic systemic treatment and anti-TNF treatment were also performed by country. Finally, we described the type of infection,[29,30] occurring in children exposed to anti-TNF, nonbiologic systemic treatment and in the general population. Several infections could occur in the same individual.

Analyses were performed using SAS version 9.4, SAS Institute Inc Cary, NC, USA.

3 | RESULTS

We included 1 617 886 children, of whom 1027 were born to women with anti-TNF treatment and 9,346 to women with nonbiologic systemic treatment (Table 1). Rheumatoid arthritis was the most common indication for anti-TNF treatment (52.3%), followed by Crohn's disease (23.1%). Characteristics according to disease group, IBD or ARTPSO, are presented in Tables S4 and S5.

There was a trend towards decreasing infection rates defined by hospital admissions through the first 12 quarters of life across all studied populations (Figure 1A). The rate of antibiotic prescriptions peaked in the second year of life (Figure 1B). Adjusted by maternal age, parity, smoking, body mass index, country and calendar year, the IRR1 for first year hospital admissions for infection was 1.43 (95% CI 1.23-1.67) for anti-TNF and 1.14 (95% CI 1.07-1.21) for nonbiologic systemic treatment compared to the general population (Table 2). Adjusting for adverse birth outcomes in IRR2 attenuated the results; 1.29 (95% CI 1.11-1.50) for anti-TNF and 1.09 (95% CI 1.02-1.15) for nonbiologic systemic treatment. The outcomes were similar for the second year of life, but with lower risk estimates, whereas no risk increase was observed for the third year. For first year antibiotic prescriptions, IRR1 was 1.07 (95% CI 0.98-1.18) and IRR2 1.06 (95% CI 0.96-1.16) for anti-TNF and 1.11 (95% CI 1.07-1.14) and 1.09 (95% CI 1.06-1.12) for nonbiologic systemic treatment. Adjusting for adverse birth outcomes had little effect overall on the IRRs for antibiotics. There was a slight increase for anti-TNF in the second year, IRR2 1.17 (95% CI 1.08-1.26), and for nonbiologic systemic treatment 1.09 (95% CI 1.06-1.12). IRR1 and IRR2 were down to 1 for the third year, both for anti-TNF and for nonbiologic systemic treatment (Table 2). There was no indication of an effect modification by disease type (IBD or ARTPSO) (Tables S6 and S7). Indeed, the relative risk for third year antibiotic prescriptions was significant for IBD, and not for ARTPSO, but the difference in the relative risk in the two disease groups was not statistically significant ($P > 0.05$).

Comparing anti-TNF with nonbiologic systemic treatment as the reference, there was a significantly increased IRR1 and IRR2 for first year hospital admissions, 1.25 (95% CI 1.06-1.48) and 1.18 (95% CI 1.00-1.40), with no other comparisons being significantly different (Table 3).

TABLE 1 Maternal characteristics among women with anti-TNF or non-biologic systemic treatment at any time during pregnancy, and women of the general population

	Anti-TNF[a]		Non-biologic systemic treatment[a]		General population[b]	
	N	(%)	N	(%)	N	(%)
Total	1027	(100)	9346	(100)	1 617 886	(100)
Maternal age						
13-19	12	(1.2)	62	(0.7)	28 149	(1.7)
20-24	88	(8.6)	720	(7.7)	213 597	(13.2)
25-29	272	(26.5)	2736	(29.3)	490 642	(30.3)
30-34	355	(34.6)	3559	(38.1)	555 108	(34.3)
35 or more	300	(29.2)	2269	(24.3)	330 374	(20.4)
Missing	0	(0.0)	0	(0.0)	16	(0.0)
Maternal age						
Median	31.0		31.0		30.0	
Mean (SD)	31.4 (5.1)		31.1 (4.8)		(30.1 (5.2)	
Parity						
0	537	(52.3)	4183	(44.8)	709 030	(43.8)
1 or more	484	(47.1)	5132	(54.9)	900 310	(55.6)
Missing	6	(0.6)	31	(0.3)	8546	(0.5)
Maternal smoking[c]						
Nonsmoker	906	(88.2)	8364	(89.5)	1 398 714	(86.5)
Smoker	98	(9.5)	725	(7.8)	169 493	(10.5)
Missing	23	(2.2)	257	(2.7)	49 679	(3.1)
Maternal body mass index[c]						
11.0-19.9	133	(13.0)	1147	(12.3)	183 510	(11.3)
20.0-24.9	489	(47.6)	4685	(50.1)	786 688	(48.6)
25.0-29.9	219	(21.3)	1905	(20.4)	351 317	(21.7)
30.0 or more	127	(12.4)	1027	(11.0)	185 137	(11.4)
Missing	59	(5.7)	582	(6.2)	111 234	(6.9)
Maternal disease						
Rheumatoid arthritis	537	(52.3)	2000	(21.4)	-	-
Ankylosing spondylitis	65	(6.3)	256	(2.7)	-	-
Psoriatic arthritis	71	(6.9)	420	(4.5)	-	-
Psoriasis	34	(3.3)	249	(2.7)	-	-
Ulcerative colitis	83	(8.1)	4533	(48.5)	-	-
Crohn's disease	237	(23.1)	1888	(20.2)	-	-
Missing	0	(0.0)	0	(0.0)	-	-
Country						
Denmark	286	(27.8)	2372	(25.4)	460 998	(28.5)
Finland	136	(13.2)	2566	(27.5)	396 024	(24.5)
Sweden	605	(58.9)	4408	(47.2)	760 864	(47.0)
Treatment period anti-TNF[d]						
Before third trimester	727	(70.8)	-	-	-	-
During third trimester	300	(29.2)	-	-	-	-
Anti-TNF agent						
Adalimumab	256	(24.9)	-	-	-	-
Certolizumab	9	(0.9)	-	-	-	-

(Continues)

TABLE 1 (Continued)

	Anti-TNF[a]		Non-biologic systemic treatment[a]		General population[b]	
	N	(%)	N	(%)	N	(%)
Etanercept	509	(49.6)	-	-	-	-
Golimumab	11	(1.1)	-	-	-	-
Infliximab	208	(20.3)	-	-	-	-
Multiple	34	(3.3)	-	-	-	-
Nonbiologic systemic treatment[e]						
Anti-malarials	45	4.4	403	4.3		
Azathioprine	117	11.4	1678	18.0		
Ciclosporine	14	1.4	75	0.8		
Corticosteroids	522	50.8	3627	38.8		
Mercaptopurine	7	0.7	130	1.4		
Methotrexate	31	3.0	101	1.1		
Mycophenolic acid	0	0.0	4	0.0		
Leflunomide	1	0.1	2	0.0		
Sulfasalazine	222	21.6	6768	72.4		
Tacrolimus	0	0.0	6	0.1		
Tioguanine	0	0.0	1	0.0		
Birth outcomes						
Preterm birth	128	(12.5)	786	(8.4)	74 981	(4.6)
Small for gestational age	49	(4.8)	270	(2.7)	35 260	(2.2)
Caesarean section	387	(37.7)	2560	(27.4)	281 654	(17.4)

[a] Treatment within 90 days before first day of last menstrual period until delivery.

[b]Women without the diseases of interest and without treatment.

[c]Measured at first prenatal visit in first trimester.

[d]Before third trimester = Treatment in the period from 90 days before first day of last menstrual period to end of second trimester. During third trimester = Treatment in the third trimester with or without earlier treatment. Twelve women were treated in the third trimester without having been previously treated in pregnancy.

[e]There were no exposures to cyclophosphamide, hydroxycarbamide, acitretin or alitretinoin. There was only leflunomide exposure in the 90 days before first day of last menstrual period. Eight women with anti-TNF and 24 women with nonbiologic systemic treatment had filled a prescription of methotrexate after first day of last menstrual period, and one woman had filled a prescription of mycophenolic acid.

For individual anti-TNF agents compared to the general population, the IRR1 was 1.35 (95% CI 1.00-1.83) for adalimumab, 1.37 (95% CI 1.05-1.78) for etanercept and 1.50 (95% CI 1.13-1.98) for infliximab, for first year hospitalisations, with attenuated results when adjusting for adverse birth outcomes in IRR2. The IRR1s was 1.16 (95% CI 1.00-1.35), 1.24 (95% CI 1.10-1.40) and 1.12 (95% CI 0.98-1.28) for second year antibiotics (Table S8). There were too few exposed to golimumab and certolizumab-pegol to perform any formal analyses.

Anti-TNF monotherapy and anti-TNF combined with nonbiologic systemic treatment were equally associated with first year admissions for infection, IRR1 1.44 (95% CI 1.13-1.82), and 1.43 (95% CI 1.17-1.74), respectively (Table 4), and IRR 2 1.38 (95% CI 1.09-1.75) and 1.24 (95% CI 1.02-1.51) when adjusting for adverse birth outcomes. Although the IRR was slightly higher for second year admissions for infection and antibiotics, the overall pattern did not represent a consistently increased risk associated with combination therapy. The risks were not increased for combination therapy for third year admissions and there was a higher risk for first year antibiotics for monotherapy.

The IRR1 for hospital admission for infection in the first year of life was 1.51 (95% CI 1.25-1.82) for anti-TNF before the third trimester only, and 1.30 (95% CI 1.00-1.69) for third trimester anti-TNF, while it was 1.23 (95% CI 0.89-1.71) and 1.36 (95% CI 0.91-2.04), for second year admissions and 1.21 (95% CI 1.10-1.33) and 1.16 (95% CI 1.03-1.32) for second year antibiotics (Table 5). Again, adjusting for adverse birth outcomes attenuated the associations, only leaving treatment before the third trimester significantly associated with first year admissions for infection and second year antibiotics. Tables S9 & S10 present these analyses stratified by maternal disease type IBD/ARTPSO with a similar pattern for both. Third trimester treatment was associated with an increased risk for second year admissions in children to mothers with ARTPSO, but with a wide confidence interval, and based on 11 events. The risk estimates for first year admissions for infection were higher for anti-TNF treatment before the third trimester only, as compared to non-biologic systemic treatment (Table 3).

Stratifying the analyses comparing anti-TNF treatment with the general population and with full adjustment in IRR2, the

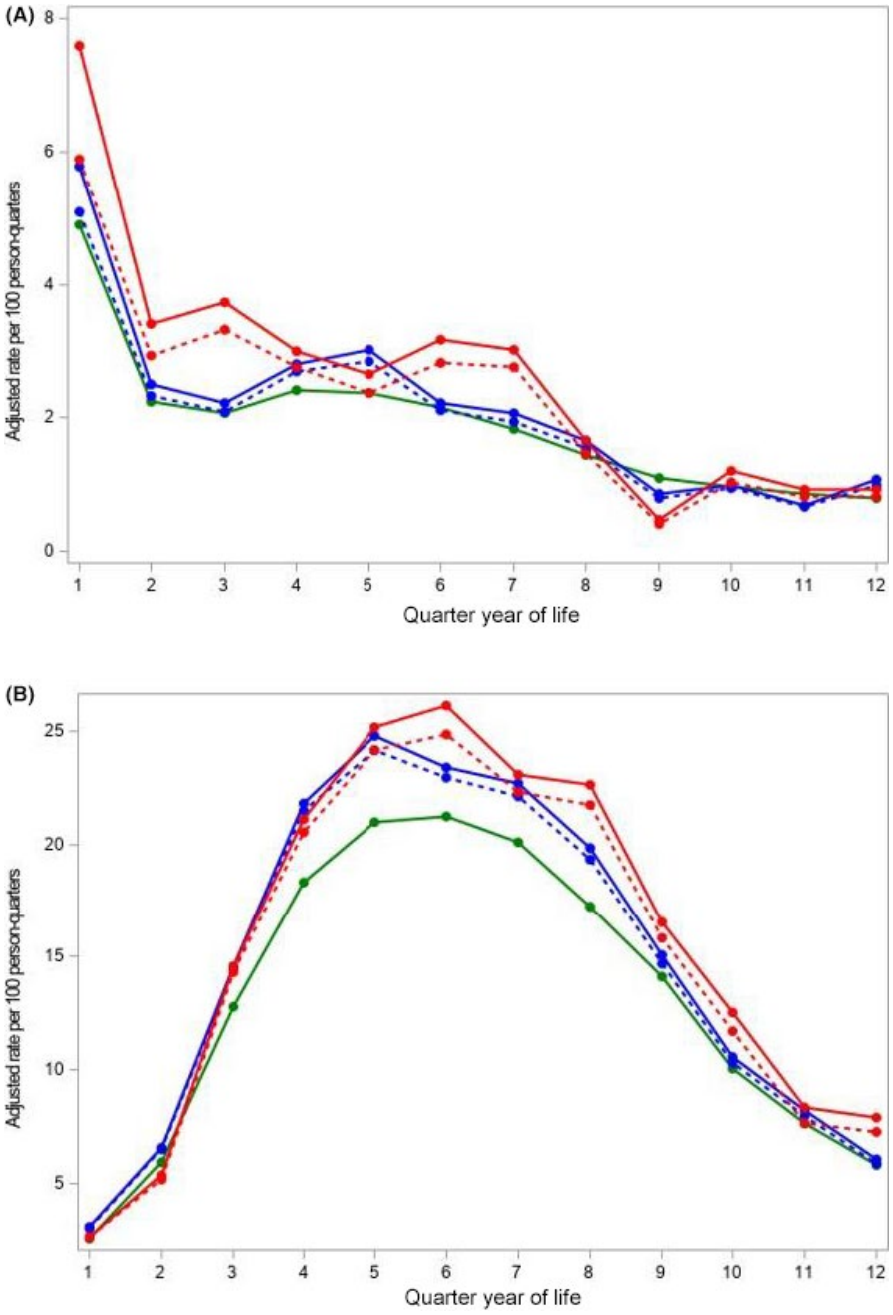

FIGURE 1 Adjusted incidence rate for (A) hospital admissions for infection and (B) antibiotic prescriptions per 100 person-quarters for anti-TNF (red), nonbiologic systemic treatment (blue) and general population (green). [Correction added on August 12, 2020, after first online publication: The labels for the X axes in Figures 1A and 1B have been revised.]

country-specific results for first year admissions for infection were 1.52 (95% CI 1.26-1.84) for Denmark, 1.52 (95% CI 1.00-2.31) for Finland and 0.93 (95% CI 0.70-1.25) for Sweden (Table S11). For all other comparisons between anti-TNF treatment and the general population, and nonbiologic systemic treatment and the general population, the results were similar for the three countries. Finally, there was no distinct pattern of type of infection (Table S12).

4 | DISCUSSION

In this three-country population-based study on paediatric infections after maternal anti-TNF treatment in pregnancy, we found slightly increased rates of paediatric infections as defined by hospital admissions for infection in the first year of life, as well as increased rates for antibiotic prescriptions in the second year of life. However, the IRRs for infections were similarly increased when considering treatment before the third trimester only or treatment in the third trimester, and was not consistently higher with combination therapy. Also, nonbiologic systemic treatment exhibited a similar association, only subtly differing from anti-TNF treatment for first year admissions for infection. There was no marked difference among adalimumab, etanercept and infliximab, and there was no distinct pattern for type of infection.

Anti-TNF treatment affects the risk of infections,[10,11] and by placental transfer, this effect may be transferred to the child. The results from observational studies are conflicting. One study reported that anti-TNF treatment in combination with other immunomodulators, but not as monotherapy, was associated with an increase in paediatric

TABLE 2 Incidence rate ratios for hospital admissions for infection and antibiotic prescriptions for infants with maternal exposure at any time during pregnancy (90 days before first day of last menstrual period until delivery) to anti-TNF and nonbiologic systemic treatment compared to the general population

Outcome	Year of life	Exposure	N	Events	Rate	IRR[a]	95% CI	IRR1[b]	95% CI	IRR2[c]	95% CI
Infections	First year	General population	1 617 886	179 939	11.2	1.00	Ref.	1.00	Ref.	1.00	Ref.
		Nonbiologic systemic treatment	9346	1126	12.1	1.08	(1.02-1.15)	1.14	(1.07-1.21)	1.09	(1.02-1.15)
		Anti-TNF	1027	169	16.5	1.40	(1.20-1.63)	1.43	(1.23-1.67)	1.29	(1.11-1.50)
	Second year	General population	1 063 487	81 033	7.6	1.00	Ref.	1.00	Ref.	1.00	Ref.
		Nonbiologic systemic treatment	5790	475	8.2	1.06	(0.97-1.17)	1.13	(1.03-1.24)	1.07	(0.97-1.18)
		Anti-TNF	708	70	9.9	1.20	(0.94-1.54)	1.28	(0.99-1.65)	1.14	(0.89-1.47)
	Third year	General population	906 164	32 706	3.6	1.00	Ref.	1.00	Ref.	1.00	Ref.
		Nonbiologic systemic treatment	4858	158	3.3	0.88	(0.75-1.03)	0.96	(0.81-1.14)	0.91	(0.76-1.07)
		Anti-TNF	539	19	3.5	0.96	(0.61-1.53)	0.95	(0.57-1.58)	0.84	(0.50-1.39)
Antibiotics	First year	General population	1 617 886	710 487	44.0	1.00	Ref.	1.00	Ref.	1.00	Ref.
		Nonbiologic systemic treatment	9346	4530	48.6	1.09	(1.06-1.12)	1.11	(1.07-1.14)	1.09	(1.06-1.12)
		Anti-TNF	1027	403	39.4	0.93	(0.85-1.02)	1.07	(0.98-1.18)	1.06	(0.96-1.16)
	Second year	General population	1 063 487	753 765	71.1	1.00	Ref.	1.00	Ref.	1.00	Ref.
		Nonbiologic systemic treatment	5790	4402	76.3	1.06	(1.04-1.09)	1.10	(1.07-1.13)	1.09	(1.06-1.12)
		Anti-TNF	708	547	77.5	1.07	(1.00-1.15)	1.19	(1.11-1.29)	1.17	(1.08-1.26)
	Third year	General population	906 164	311 297	34.6	1.00	Ref.	1.00	Ref.	1.00	Ref.
		Nonbiologic systemic treatment	4858	1693	35.1	1.02	(0.97-1.07)	1.05	(1.00-1.10)	1.04	(0.99-1.09)
		Anti-TNF	539	193	36.0	1.00	(0.87-1.15)	1.10	(0.95-1.27)	1.07	(0.93-1.24)

[a]Crude.

[b]IRR1 Adjusted for age, parity, smoking, body mass index, year of birth, country and the interaction between year of birth and country.

[c]IRR2 Additionally adjusted for preterm birth, small for gestational age, low birth weight and caesarean section.

TABLE 3 Incidence rate ratios for hospital admissions for infection and antibiotic prescriptions for children with maternal exposure to anti-TNF (a) at any time during pregnancy (90 days before first day of last menstrual period until delivery), and (b) before the third trimester only, or during the third trimester of pregnancy, with or without earlier treatment. Nonbiologic systemic treatment as the reference

Outcome	Exposure	IRR1[a]			IRR2[b]		
		First year	Second year	Third year	First year	Second year	Third year
Infections	Anti-TNF vs Nonbiologic systemic treatment	1.25 (1.05-1.48)	1.13 (0.85-1.48)	0.98 (0.57-1.69)	1.18 (1.00-1.40)	1.05 (0.80-1.39)	0.91 (0.53-1.57)
	Anti-TNF before the 3rd trimester vs Nonbiologic systemic treatment	1.31 (1.07-1.61)	1.08 (0.76-1.53)	0.93 (0.47-1.84)	1.24 (1.01-1.52)	1.01 (0.72-1.43)	0.87 (0.44-1.72)
	Anti-TNF during the 3rd trimester vs Nonbiologic systemic treatment	1.14 (0.87-1.50)	1.21 (0.79-1.84)	1.08 (0.46-2.52)	1.08 (0.82-1.41)	1.12 (0.74-1.70)	1.00 (0.43-2.32)
Antibiotics	Anti-TNF vs Nonbiologic systemic treatment	0.97 (0.88-1.07)	1.08 (0.99-1.17)	1.04 (0.89-1.21)	0.96 (0.87-1.06)	1.06 (0.98-1.15)	1.03 (0.88-1.20)
	Anti-TNF before the 3rd trimester vs Nonbiologic systemic treatment	0.97 (0.86-1.10)	1.09 (0.99-1.21)	1.01 (0.84-1.22)	0.97 (0.86-1.09)	1.09 (0.98-1.20)	1.01 (0.84-1.21)
	Anti-TNF during the 3rd trimester vs Nonbiologic systemic treatment	0.96 (0.82-1.13)	1.04 (0.91-1.18)	1.10 (0.86-1.41)	0.95 (0.81-1.12)	1.02 (0.90-1.16)	1.07 (0.83-1.37)

[a]IRR1 Adjusted for age, parity, smoking, body mass index, year of birth, country, the interaction between year of birth and country and chronic inflammatory diagnosis.
[b]IRR2 Additionally adjusted for preterm birth, small for gestational age, low birth weight and caesarean section.

infections at age 9-12 months, and Juulsgaard et al reported that the risk of infection was significantly increased in combination therapy vs monotherapy in a cohort of 80 women with IBD.[16,18] A 2018 French study reported no increased risk of paediatric infections in a large cohort of women with IBD.[9] A study by Vinet et al could not detect any marked increased risk for serious infections in children to women with RA exposed to anti-TNF during pregnancy, including exposure in the third trimester.[21] A recent multicentre study with a mean follow-up of 4 years reported no increase in hospital admission paediatric infections for children to women with IBD who had been treated with anti-TNF compared to women with IBD without anti-TNF or thiopurines, and with a relative risk of 1.2 (95% CI 0.8-1.8).[19] In the current study, the IRR for hospital admission infections in the first year of life was 1.19 (95% CI 1.01-1.40) comparing anti-TNF versus nonbiologic systemic treatment.

We observed an increased rate of infections early in life, which decreased across 3 years of follow-up. A persistent effect of anti-TNF agents on the immune system has been proposed previously.[18] Two smaller studies have more specifically assessed changes in infant lymphocyte maturation, with one reporting persisting effects up to 12 months of age until they were normalised.[31,32] It is, however, important to point out that little is known about the effect of immunomodulatory drugs, or even inflammatory disease itself, on the intrauterine development of the immune system.

Another factor related to treatment and disease is that both immunomodulatory treatment and inflammatory disease may affect the healthcare-seeking behaviour of patients and their children. Also, healthcare professionals may consider treatment a risk factor for infections, resulting in a higher likelihood of a hospital admission or antibiotic prescription. Indeed, the concern for paediatric infections after maternal anti-TNF treatment has been a recurring topic of the research community. Anti-TNF treatment is typically prescribed to patients with severe disease, thus selecting a group of women where this bias towards detecting more events could play a larger role. The observation that the risks were significantly increased for anti-TNF and nonbiologic systemic treatment particularly for *first year* admissions for infection but for *second year* antibiotics, we hypothesise mirrors the pattern of when these events typically peak in all included cohorts, as seen in Figure 1 A and B. This likely increases the statistical power in the analyses, but also amplifies effects of behaviour and disease characteristics.

Detection bias may also come into play in children with adverse birth outcomes such as preterm birth, small for gestational age and caesarean section, which both IBD and ARTPSO have been associated with. Moreover, adverse birth outcomes are associated with paediatric infections,[33,34] and may be considered in the causal pathway between exposure and outcome. A mediator in the causal pathway should not be adjusted for if the total association is aimed at. However, since some of the associations remained significant after such adjustment, our analyses support a direct association between anti-TNF treatment and the infection-related outcomes under study. Stratifying these analyses by country, we found increased risk estimates for Finland and Denmark for first year hospitalisations, but otherwise similar results. It may be that there are country-specific differences in the guidelines regarding hospitalisations

TABLE 4 Incidence rate ratios for hospital admissions for infection and antibiotic prescriptions for infants with maternal exposure to anti-TNF at any time during pregnancy (90 days before first day of last menstrual period until delivery) as monotherapy and as combination therapy with nonbiologic systemic treatment compared to the general population

Outcome	Year of life	Exposure	N	Events	Rate	IRR[a]	95% CI	IRR1[b]	95% CI	IRR2[c]	95% CI
Infections	First year	General population	1 617 886	179 939	11.2	1.00	Ref.	1.00	Ref.	1.00	Ref.
		Monotherapy anti-TNF	353	64	18.2	1.60	(1.26-2.04)	1.44	(1.13-1.82)	1.38	(1.09-1.75)
		Combination anti-TNF and nonbiologic systemic treatment	674	105	15.6	1.29	(1.06-1.57)	1.43	(1.17-1.74)	1.24	(1.02-1.51)
	Second year	General population	1 063 487	81 033	7.6	1.00	Ref.	1.00	Ref.	1.00	Ref.
		Monotherapy anti-TNF	254	25	9.9	1.00	(0.63-1.58)	0.93	(0.59-1.49)	0.91	(0.57-1.45)
		Combination anti-TNF and nonbiologic systemic treatment	454	45	9.9	1.32	(0.98-1.77)	1.52	(1.13-2.06)	1.28	(0.95-1.73)
	Third year	General population	906 164	32 706	3.6	1.00	Ref.	1.00	Ref.	1.00	Ref.
		Monotherapy anti-TNF	180	9	5.0	1.21	(0.60-2.45)	1.11	(0.51-2.38)	1.06	(0.49-2.28)
		Combination anti-TNF and nonbiologic systemic treatment	359	10	2.8	0.84	(0.45-1.55)	0.86	(0.43-1.71)	0.72	(0.36-1.43)
Antibiotics	First year	General population	1 617 886	710 487	44.0	1.00	Ref.	1.00	Ref.	1.00	Ref.
		Monotherapy anti-TNF	353	154	43.9	1.05	(0.90-1.21)	1.19	(1.03-1.38)	1.18	(1.02-1.36)
		Combination anti-TNF and nonbiologic systemic treatment	674	249	37.1	0.87	(0.77-0.99)	1.01	(0.90-1.14)	1.00	(0.88-1.12)
	Second year	General population	1 063 487	753 765	71.1	1.00	Ref.	1.00	Ref.	1.00	Ref.
		Monotherapy anti-TNF	254	207	81.8	1.08	(0.96-1.22)	1.13	(1.00-1.28)	1.12	(0.99-1.26)
		Combination anti-TNF and nonbiologic systemic treatment	454	340	75.1	1.07	(0.98-1.17)	1.23	(1.12-1.36)	1.20	(1.09-1.32)
	Third year	General population	906 164	311 297	34.6	1.00	Ref.	1.00	Ref.	1.00	Ref.
		Monotherapy anti-TNF	180	88	49.2	1.18	(0.96-1.46)	1.20	(0.96-1.50)	1.18	(0.95-1.48)
		Combination anti-TNF and nonbiologic systemic treatment	359	105	29.4	0.91	(0.76-1.10)	1.05	(0.87-1.26)	1.02	(0.84-1.23)

[a]Crude.

[b]IRR1 Adjusted for age, parity, smoking, body mass index, year of birth, country and the interaction between year of birth and country.

[c]IRR2 Additionally adjusted for preterm birth, small for gestational age, low birth weight and caesarean section.

TABLE 5 Incidence rate ratios for hospital admission for infection and antibiotic prescriptions for infants with maternal exposure to anti-TNF before the third trimester only (90 days before first day of last menstrual period until start of third trimester), or during the third trimester of pregnancy, with or without earlier treatment, compared to the general population

Outcome	Year of life	Exposure	N	Events	Rate	IRR1[a]	(95% CI)	IRR2[b]	(95% CI)
Infections	First year	General population	1 617 886	179 939	11.2	1.00	Ref.	1.00	Ref.
		Before third trimester	727	115	15.9	1.51	(1.25-1.82)	1.36	(1.13-1.64)
		During third trimester	300	54	18.0	1.30	(1.00-1.69)	1.17	(0.91-1.52)
	Second year	General population	1 063 487	81 033	7.6	1.00	Ref.	1.00	Ref.
		Before third trimester	505	43	8.5	1.23	(0.89-1.71)	1.10	(0.80-1.52)
		During third trimester	203	27	13.3	1.36	(0.91-2.04)	1.20	(0.80-1.79)
	Third year	General population	906 164	32 706	3.6	1.00	Ref.	1.00	Ref.
		Before third trimester	391	14	3.6	0.90	(0.47-1.74)	0.80	(0.42-1.53)
		During third trimester	148	5	3.4	1.04	(0.45-2.39)	0.91	(0.40-2.07)
Antibiotics	First year	General population	1 617 886	710 487	44.0	1.00	Ref.	1.00	Ref.
		Before third trimester	727	270	37.4	1.07	(0.96-1.20)	1.06	(0.95-1.19)
		During third trimester	300	133	44.4	1.07	(0.92-1.26)	1.05	(0.90-1.24)
	Second year	General population	1 063 487	753 765	71.1	1.00	Ref.	1.00	Ref.
		Before third trimester	505	376	74.7	1.21	(1.10-1.33)	1.19	(1.08-1.30)
		During third trimester	203	171	84.5	1.16	(1.03-1.32)	1.13	(0.99-1.28)
	Third year	General population	906 164	311 297	34.6	1.00	Ref.	1.00	Ref.
		Before third trimester	391	128	32.9	1.07	(0.89-1.27)	1.05	(0.88-1.26)
		During third trimester	148	65	44.2	1.18	(0.92-1.50)	1.13	(0.88-1.44)

[a]IRR1 Adjusted for age, parity, smoking, body mass index, year of birth, country, the interaction between year of birth and country and chronic inflammatory diagnosis.

[b]IRR2 Additionally adjusted for preterm birth, small for gestational age, low birth weight and caesarean section.

for infection in exposed children that are more distinct in the first year of life.

There was also an increased rate of infections after nonbiologic systemic treatment compared to the general population. Most of these agents are transferred across the placenta,[35,36] but it is uncertain if this affects the child's susceptibility to infections. For nonbiologic systemic treatment, health-seeking behaviour may confound the result as for anti-TNF, but there may also be a true effect which needs to be further explored. Combination therapy was, however, not consistently associated with higher infection rates than monotherapy in the current study, thus not supporting an added effect of nonbiologic systemic treatment to anti-TNF.

We found no convincing and consistent differences between anti-TNF treatment before the third trimester only or with treatment during the third trimester. We did observe increased risks for late treatment and second year hospital admissions in the ARTPSO subgroup, but instead the results for earlier treatment reached statistical significance for first year admissions and second year antibiotics in both adjustment models for the whole anti-TNF group. Since the anti-TNF agents are not transferred across the placenta in significant amounts until later in pregnancy, another mechanism than the active transport of anti-TNF antibodies may come into play associating treatment before the third trimester with paediatric infections, but can as far as we know only be speculated about.

4.1 | Strengths and limitations

Using national health register data from three countries, we were able to collect a large study population including over 1000 exposed children and presented results for all anti-TNF as well as for the most common agents separately. The data were prospectively collected, eliminating recall bias. We were unable to shape the data being collected to include disease-specific variables on activity and severity. Moreover, register data do not ascertain that exposure actually took place. However, these are costly drugs that require refrigeration, and are likely taken as prescriptions are filled. Some administration of anti-TNF is not recorded as filled prescriptions in registers, particularly intravenous administration. Although we had some additional data from the disease-specific registers, some women treated with anti-TNF may have been classified as untreated. We did not have data to assess treatment in more detail than by trimester. On the other hand, we followed the children up to 3 years of age and assessed the infection rates over time. We lacked information on breastfeeding, which may affect (a) the child's exposure to maternal treatment, although anti-TNF agents are not transferred to breast milk to any large extent and are not well absorbed from the gastrointestinal tract,[37] and (b) the child's immunocompetence by the transfer of maternal IgA antibodies.[38] We also lacked information on maternal infections, which may be transferred to the child during pregnancy, delivery or during the child's first years.

5 | CONCLUSIONS

Maternal treatment with anti-TNF during pregnancy was associated with an increase in paediatric infections, particularly in the first year of life, compared to nonbiologic systemic treatment and to the general population. However, the increased risks observed for anti-TNF were small and decreased with increasing age. They were present even without treatment in the third trimester and were not further increased with nonbiologic systemic treatment combination therapy, even though nonbiologic systemic treatment in itself was associated with an increased risk of paediatric infections. In conclusion, these are reassuring results, supporting continued treatment in the third trimester, particularly if the alternative is a risk of disease relapse in the pregnant woman.

6 | ETHICS APPROVAL

The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (Record 2006/889:31), by THL Finnish Institute for Health and Welfare (1636/6.02.00/2018) and Social Insurance Institution of Finland, Kela (126_522_2018) in Finland and by the Danish Data Protection Agency (Record 2014-41-3593).

ACKNOWLEDGEMENTS

GB was supported by the Stockholm Region (clinical postdoctoral appointment).

Declaration of personal interests: GB and HK did not receive personal fees, honoraria, grants or consultancies. Centre for Pharmacoepidemiology at Karolinska institutet is, however, involved in several studies with funding from various companies, mainly post-marketing follow-up studies. HTS and LP did not receive personal fees, honoraria, grants or consultancies. Department of Clinical Epidemiology at Aarhus University is involved in studies with funding from various companies as grants to and administered by Aarhus University. KH reported receiving personal fees to give lectures for UCB Pharma and Abbvie. HK, MG and MKL have received a grant from Innovative Medicines Initiative during preparation of this manuscript. AE, MSE and FG did not receive personal fees to pose a conflict of interest in this study.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

How to cite this article: Bröms G, Kieler H, Ekbom A, et al. Paediatric infections in the first 3 years of life after maternal anti-TNF treatment during pregnancy. *Aliment Pharmacol Ther*. 2020;52:843–854. https://doi.org/10.1111/apt.15971

APPENDIX 1

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