Maternal Antibiotic Use During Pregnancy and Type 1 Diabetes in Children—A National Prospective Cohort Study

https://doi.org/10.2337/dc18-1764

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Prenatal prescription of antibiotics is common but may perturb the composition of the intestinal microbiota in the offspring. In childhood the latter may alter the developing immune system to affect the pathogenesis of type 1 diabetes (1). Previous epidemiological studies reported conflicting results regarding the association between early exposure to antibiotics and childhood type 1 diabetes (2,3). Here we investigated the association in a Danish register setting.

The Danish National Birth Cohort (DNBC) provided data from 100,418 pregnant women recruited between 1996 and 2002 and their children born between 1997 and 2003 (n = 96,840). The women provided information on exposures during and after pregnancy. Antibiotic prescription during pregnancy was obtained from the Danish National Prescription Registry (anatomical therapeutic chemical code J01), and type 1 diabetes diagnoses (diagnostic codes DE10 and DE14) during childhood and adolescence were obtained from the Danish National Patient Register. The children were followed until 2014 (mean follow-up time 14.3 years [range 11.5–18.4 years, SD 1.4]). We excluded (n = 4,828) twins and triplets, children born before gestational week 26, children weighing <500 g at birth, and stillbirths, leaving 92,012 children for unadjusted analyses. Socioeconomic status, parity, maternal diabetes, smoking during pregnancy, or cesarean section were unknown in 16,383 individuals, leaving 75,629 for adjusted analyses. Antibiotics were classified into the following categories: penicillins, β-lactam antibacterials; sulfonamides and trimethoprim; macrolides, lincosamides, and streptogramins; and narrow- or broad-spectrum antibiotics. Broad-spectrum antibiotics were further classified as ampicillin, amoxicillin, and sulfamethizole. Risk of childhood type 1 diabetes according to maternal use of antibiotics during pregnancy was assessed by Cox regression using the SAS software package, version 9.4 (SAS Institute Inc.). A P value <0.05 was considered statistically significant.

A total of 336 children developed type 1 diabetes during follow-up. Neither overall exposure (hazard ratio [HR] 0.90; 95% CI 0.68–1.18), number of courses (HR 0.36–0.97; see Table 1), nor trimester-specific exposure (HR 0.81–0.89; see Table 1) of antibiotics in utero was associated with childhood diabetes. Moreover, exposure to specific types of antibiotics in utero did not change the risk of childhood type 1 diabetes: penicillins, β-lactam antibacterials (HR 0.94; 95% CI 0.69–1.27); sulfonamides or trimethoprim (HR 0.81; 95% CI 0.43–1.53); macrolides, lincosamides, and streptogramins (HR 0.74; 95% CI 0.30–1.79) in the group of ever users; penicillins, β-lactam antibacterials (HR 0.93; 95% CI 0.69–1.27) and macrolides, lincosamides, and streptogramins (HR 0.64; 95% CI 0.24–1.72) in the group that only used a specific type of antibiotic (only users) (Table 1). Neither narrow- (HR 0.95; 95% CI 0.69–1.31) nor broad-spectrum (HR 0.79; 95% CI 0.50–1.25) antibiotics in utero were associated with childhood type 1 diabetes. No association was found among ever users between in utero exposure to ampicillin (HR 0.86; 95% CI 0.42–1.74) or sulfamethizole (HR 0.82; 95% CI 0.43–1.54) and childhood diabetes (Table 1).

Exposure to antibiotics in utero was not associated with childhood type 1 diabetes but tended to be associated with protection, although not reaching statistical significance. This concurs with a study in nonobese diabetic mice, a model of type 1 diabetes, showing that mice exposed to antibiotics (neomycin, polymyxin B, and streptomycin) in utero were protected from autoimmune diabetes, possibly due to increased proportions of regulatory T cells (4). Interestingly,

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Received 20 August 2018 and accepted 8 September 2018.

Table 1—HRs of the association between the use of antibiotics during pregnancy and childhood type 1 diabetes

Exposure	HR (95% CI) for type 1 diabetes, unadjusted (N† = 92,012)	HR (95% CI) for type 1 diabetes, adjusted* (N† = 75,629)
Antibiotics during pregnancy		
Yes	0.95 (0.74–1.22)	0.90 (0.68–1.18)
No	1.00	1.00
Antibiotic courses during pregnancy		
1	1.00 (0.76–1.31)	0.97 (0.71–1.31)
2	0.93 (0.55–1.57)	0.82 (0.45–1.51)
≥3	0.48 (0.15–1.49)	0.36 (0.09–1.44)
0	1.00	1.00
Antibiotics in first trimester		
Yes	0.92 (0.63–1.14)	0.85 (0.55–1.31)
No antibiotics during pregnancy	1.00	1.00
Antibiotics in second trimester		
Yes	1.01 (0.72–1.41)	0.89 (0.60–1.32)
No antibiotics during pregnancy	1.00	1.00
Antibiotics in third trimester		
Yes	0.82 (0.56–1.20)	0.81 (0.53–1.23)
No antibiotics during pregnancy	1.00	1.00
Antibiotics during pregnancy by type, ever users		
Penicillins, β-lactam antibacterials (J01C)	0.96 (0.73–1.27)	0.94 (0.69–1.27)
Sulfonamides and trimethoprim (J01E)	1.03 (0.61–1.74)	0.81 (0.43–1.53)
Macrolides, lincosamides, and streptogramins (J01F)	0.73 (0.32–1.63)	0.74 (0.30–1.79)
No antibiotics during pregnancy	1.00	1.00
Antibiotics during pregnancy by type, only users‡		
Penicillins, β-lactam antibacterials (J01C)	0.96 (0.73–1.27)	0.93 (0.69–1.27)
Sulfonamides and trimethoprim (J01E)	–§	–§
Macrolides, lincosamides, and streptogramins (J01F)	0.67 (0.28–1.61)	0.64 (0.24–1.72)
No antibiotics during pregnancy	1.00	1.00
Narrow- or broad-spectrum antibiotics during pregnancy		
Narrow-spectrum antibiotics	1.00 (0.75–1.33)	0.95 (0.69–1.31)
Broad-spectrum antibiotics	0.86 (0.57–1.28)	0.79 (0.50–1.25)
No antibiotics during pregnancy	1.00	1.00
Type of broad-spectrum antibiotics during pregnancy, ever users		
Ampicillin (J01CA01, J01CA02, J01CA06)	0.80 (0.41–1.55)	0.86 (0.42–1.74)
Amoxicillin (J01CA04, J01CR02)	–§	–§
Sulfamethizole (J01EB02)	1.04 (0.62–1.74)	0.82 (0.43–1.54)
No antibiotics during pregnancy	1.00	1.00

*The HRs were adjusted for maternal prepregnancy BMI, paternal BMI, maternal age at conception, socioeconomic status, parity, maternal diabetes, smoking during pregnancy, birth weight, and gestational weight gain. †N is the total number of individuals included in the analyses. ‡Analyses based on subgroups who had only used the same type of antibiotics; these women were compared with women who had not used antibiotics during pregnancy. §Too few cases for analysis.

in our study gestational diabetes was not reported in any mothers with children with type 1 diabetes but was reported in 0.7% of mothers with healthy children. Although the difference is small and statistically nonsignificant, it suggests that gestational diabetes may have a protective effect. This is in line with a previous study demonstrating that early stimulation of β-cells reduces the incidence of autoimmune diabetes in the BB rat model of type 1 diabetes (5) and may support the hypothesis that β-cells mature when stimulated perinatally, which protects the child against type 1 diabetes.

In Denmark, purchasing antibiotics requires a prescription, and all purchases are registered at the Danish National Prescription Registry. However, the use of antibiotics may have been overestimated because of the possibility of filled but unused prescriptions, although unused antibiotics that were returned were not included in the analysis. Maternal use of antibiotics during pregnancy may indicate that infection could have influenced the pathogenesis of type 1 diabetes in the fetus. However, we did not have detailed data on the underlying infections leading to prescription of antibiotics to pinpoint the potential causal factor (antibiotics or infection) for childhood type 1 diabetes.

This large prospective Danish cohort study demonstrated that maternal use of antibiotics during pregnancy was not associated with childhood type 1 diabetes. Thus, the results from this study do not support a revision of the clinical recommendations on treatment with antibiotics during pregnancy.

Funding. This article was supported by Kirsten og Freddy Johansens Fond, the Novo Nordisk

Foundation (NNFOC0017740), and the Danish Council of Independent Research (F-12815-01-76). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. K.H.A. and J.C.A. designed the study. C.S.M. performed the statistical analysis. All authors contributed to the acquisition, analysis, or interpretation of data. M.H.-J. drafted the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content and approved the final version. C.S.M. is the guarantor of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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