Antibiotic use during pregnancy alters the commensal vaginal microbiota

J. Stokholm[1,3], S. Schjørring[2], C. E. Eskildsen[3], L. Pedersen[1], A. L. Bischoff[4], N. Følsgaard[4], C. G. Carson[4], B. L. K. Chawes[4], K. Bønnelykke[4], A. Mølgaard[4], B. Jacobsson[5,6], K. A. Krogfelt[2] and H. Bisgaard[4]

1) *Copenhagen Prospective Studies on Asthma in Childhood, Health Sciences, University of Copenhagen, Naestved Hospital, Naestved,* 2) *Department of Microbiological Surveillance and Research, Statens Serum Institut,* 3) *Department of Food Science, Faculty of Life Sciences, University of Copenhagen, Copenhagen,* 4) *Copenhagen Prospective Studies on Asthma in Childhood, Health Sciences, University of Copenhagen, Copenhagen University Hospital, Gentofte, Copenhagen, Denmark,* 5) *Department of Obstetrics and Gynaecology, Sahlgrenska University Hospital/Ostra, Gothenburg, Sweden and* 6) *Division of Epidemiology, Department of Genes and Environment, Institute of Public Health, Oslo, Norway*

Abstract

Antibiotics may induce alterations in the commensal microbiota of the birth canal in pregnant women. Therefore, we studied the effect of antibiotic administration during pregnancy on commensal vaginal bacterial colonization at gestational week 36. Six hundred and sixty-eight pregnant women from the novel unselected Copenhagen Prospective Studies on Asthma in Childhood ($COPSAC_{2010}$) pregnancy cohort participated in this analysis. Detailed information on oral antibiotic prescriptions during pregnancy filled at the pharmacy was obtained and verified prospectively. Vaginal samples were obtained at pregnancy week 36 and cultured for bacteria. Women who received oral antibiotics during any pregnancy trimester had an increased rate of colonization by *Staphylococcus* species in the vaginal samples as compared with samples obtained from women without any antibiotic treatment during pregnancy (adjusted OR 1.63, 95% CI 1.06–2.52, p 0.028). Oral antibiotic administration in the third trimester were also associated with increased colonization by *Staphylococcus* species (adjusted OR 1.98, 95% CI 1.04–3.76, p 0.037). These bacteriological changes were associated with urinary tract infection antibiotics. Women treated in the third trimester of pregnancy were more often colonized by *Escherichia coli* than women without antibiotic treatment in the third trimester (adjusted OR 1.91, 95% CI 1.04–3.52, p 0.038). This change was associated with respiratory tract infection (RTI) antibiotics. We did not observe any significant changes in vaginal *Streptococcus agalactiae* (group B *streptoccocus*) or *Staphylococcus aureus* colonization following antibiotic treatment in pregnancy. Antibiotic administration during pregnancy leads to alterations in the vaginal microbiological ecology prior to birth, with potential morbidity, and long-term effects on the early microbial colonization of the neonate.

Keywords: Bacteria, *Escherichia coli*, infections, microbiome, pregnancy, *Staphylococcus*
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Corresponding author: H. Bisgaard, Copenhagen Prospective Studies on Asthma in Childhood, Health Sciences, University of Copenhagen, Copenhagen University Hospital, Gentofte, Ledreborg Allé 34, DK-2820 Gentofte, Copenhagen, Denmark
E-mail: bisgaard@copsac.com

Oral antibiotic administration during pregnancy leads to alterations in the vaginal bacterial microbiota before birth, with potential effect on the woman and fetus.

Introduction

Across various cultural and healthcare settings, antibiotics are among the most widely used drugs in pregnancy [1]. Prescribing antibiotics during pregnancy presents a challenge, as infections need to be treated, but the fetus needs to be protected from possible side effects of the drugs [2].

The composition of the commensal vaginal microbiota is not constant [3]. The commensal microbiota protects against the proliferation of pathogenic bacteria [4,5]. Numerous factors may contribute to changes in the vaginal composition, including antibiotic administration [3]. A few studies have addressed the effects of local antibiotics on the vaginal microbiota. However, these had a focus on alterations related to treatment for bacterial vaginosis and whether the antibiotic treatment was preventive for preterm birth [3,6,7].

The study objective was to analyse the effect of antibiotic use during pregnancy on vaginal colonization at week 36 of pregnancy. We hypothesized that maternal antibiotic use in pregnancy is an environmental risk factor for both short-term and long-term changes in the vaginal microbial composition.

Materials and Methods

Ethics

The study followed the principles of the Declaration of Helsinki, and was approved by the Ethics Committee for Copenhagen (H-B-2008-093) and the Danish Data Protection Agency (2008-41-2599). Written informed consent was obtained from all participants.

The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [8].

Study population

The novel Copenhagen Prospective Studies on Asthma in Childhood 2010 ($COPSAC_{2010}$) is an ongoing Danish cohort study of 738 pregnant women and their children followed prospectively from pregnancy week 24 in a protocol designed from the first COPSAC birth cohort ($COPSAC_{2000}$) [9–11]. Participants were recruited unselectively during 2009–2010, and the only exclusion criteria were chronic cardiac, endocrinological, nephrological or lung disease other than asthma. Data validation and quality control followed the guidelines for Good Clinical Practice. Data were collected during visits to the clinical research unit, and stored in a dedicated online database, double-checked against source data, and locked.

Bacterial samples

Vaginal samples from asymptomatic pregnant women were characterized by culture at pregnancy week 36. Swabs were sampled from the fornix posterior of the vagina with flocked swabs (ESWAB flocked regular; SSI Diagnostica, Hillerød, Denmark), and were cultured within 24 h according to standard methods on non-selective and selective media (SSI Diagnostica). One set of blood agar plates (5% horse blood) and chocolate agar plates (including lysed blood cells) were used for general culture. These were incubated aerobically at 37°C for 18–20 h. The other set of blood agar and chocolate agar plates were incubated under micro-aerophilic conditions (5% CO_2, 3% H_2, 5% O_2, and 87% N_2) at 37°C for 48 h. Additionally, one HBT plate was used for selection of *Gardnerella vaginalis* incubated under micro-aerophilic conditions at 37°C for 48 h. Subsequently, microbial identification was performed according to growth on selective media, characteristics of colonies, and cellular morphology. All bacterial identifications were confirmed biochemically with VITEK-2 (BioMérieux, Marcy l'Etoile, France). The isolates were characterized at the species level, and grouped in the analyses at the genus level. We used a cut-off value of <5% women colonized for a genus to be analysed. Group B *streptococcus* (GBS; *Streptococcus agalactiae*), *Escherichia coli* and *Staphylococcus aureus* were analysed at the species level.

Information on antibiotic use

Detailed information on oral antibiotic ingestion during pregnancy was obtained by interviews with the participants at the COPSAC research clinic at pregnancy weeks 24 and 36, and 1 week postpartum. This information was validated against data in the Danish Medical Agency's Register, which included records on all drug prescriptions filled at the pharmacy, to minimize recall bias and exclude antibiotics collected but not ingested.

Oral antibiotic ingestion was analysed both as a dichotomized (yes/no) and as a categorized variable by treatment indication (A—urinary tract infection (UTI) antibiotics (J01CA08, J01EBxx, and J01XExx); B—respiratory tract infection (RTI) antibiotics (J01CAxx, excluding J01CA08, J01CExx, and J01FAxx); C—other antibiotics (J01CFxx, D06BXxx, J01AAxx, and P01ABxx)). Only treatments with oral antibiotics administered before the vaginal sampling date were used in this analysis. Analyses were performed on antibiotic use at any time-point during pregnancy and on use in the third trimester of pregnancy.

Covariates

Information on race, maternal age at birth, parity, number of older siblings at home, asthma, alcohol intake, smoking, cat or dog in the home and household income during pregnancy was obtained by the study physicians during the scheduled visits to the COPSAC clinics at gestational weeks 24 and 36 and 1 week postpartum.

Statistical analysis

The chi-square test, Student's *t*-test or the Wilcoxon rank sum test was used for simple associations in the demographic