



# Antibiotics in Pregnancy Increase Children's Risk of Otitis Media and Ventilation Tubes

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**Objectives** To study the association between antibiotic intake in pregnancy and the development of otitis media and placement of ventilation tubes (VTs) in the offspring under the hypothesis that antibiotics in pregnancy may alter the offspring's propensity for disease.

**Study design** Data from the 700 children in the Copenhagen Prospective Studies on Asthma in Childhood 2010 unselected birth cohort study were used. Information on maternal antibiotic use and other exposures during pregnancy was collected prospectively from interviews and validated in national registries. Otitis media episodes were registered in a prospective diary for 3 years. Information regarding children's VTs was obtained from national registries.

**Results** There were 514 children who had diary information and were included in the analysis regarding otitis media episodes. For VTs analysis, 699 children were included. Thirty-seven percent of the mothers received antibiotics during pregnancy, and this was associated with increased risk of otitis media (adjusted hazard ratio 1.30; 95% CI 1.04-1.63;  $P = .02$ ). The risk of receiving VTs was especially associated with third trimester antibiotics (adjusted hazard ratio 1.60; 95% CI 1.08-2.36,  $P = .02$ ). The risk of otitis media increased with increasing number of treatments (per-level adjusted hazard ratio 1.20; 95% CI 1.04-1.40;  $P = .02$ ), but for VTs this association was not significant after adjustment.

**Conclusion** Maternal use of antibiotics during pregnancy is associated with an increased risk of otitis media and VT insertions in the offspring. Antibiotics late in pregnancy mainly contributed to these effects, pointing toward potential transmission of an unfavorable microbiome from mother to child. (*J Pediatr* 2017;183:153-8).

The consumption of antibiotics is increasing worldwide, causing concern in the medical community owing to increasing prevalence of bacterial antibiotic resistance and numerous potential long-term adverse health effects.<sup>1-3</sup> Often, infections are more serious if contracted in pregnancy, both for the mother and the fetus, in part owing to a suppressed maternal immune response.<sup>4,5</sup> These infections and related complications are potentially preventable with antibiotic treatment,<sup>6</sup> leaving the prescription of antibiotics during pregnancy a complex clinical decision. Antibiotics may perturb maternal bacterial colonization,<sup>7,8</sup> and a subsequent unfavorable maternal bacterial ecology may trigger lasting disease processes in perinatal life in susceptible offspring or affect the earliest colonization of the child by vertical transmission.<sup>9,10</sup>

Otitis media (OM) is one of the most common infections in early childhood.<sup>11</sup> Middle ear effusion and recurrent acute OM are often treated with ventilation tubes (VT). Some aspects of the pathogenesis of OM are well-described, including the anatomic, genetic, and infectious microbiological components,<sup>12-17</sup> whereas others remain obscure, including environmental triggers of disease susceptibility.

The objective of this study was to analyze the effect of maternal antibiotic intake during pregnancy on the risk of OM and VTs in early childhood. We hypothesized that antibiotic consumption in pregnancy can increase the child's risk of OM, and examined possible mechanisms by analyzing effects of treatment in different pregnancy trimesters, number of treatments and furthermore treatment after birth.

## Methods

The Copenhagen Prospective Studies on Asthma in Childhood 2010 cohort (COPSAC<sub>2010</sub>)<sup>18</sup> is an ongoing unselected birth cohort where mothers were recruited at pregnancy week 24 in 2008-2010. It is a single-center study. Exclusion criteria were maternal chronic cardiac, endocrine, renal, or pulmonary disease other

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aHR	Adjusted hazard ratio
COPSAC <sub>2010</sub>	Copenhagen Prospective Studies on Asthma in Childhood 2010
OM	Otitis media
RTI	Respiratory tract infection
UTI	Urinary tract infection
VT	Ventilation tubes

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than asthma. Seven hundred children were included at 1 week of age and were followed prospectively by study pediatricians with scheduled visits at 1 week, and 1, 3, 6, 12, 18, 24, 30, and 36 months of age.

The study was conducted in accordance with the guiding principles of the Declaration of Helsinki and was approved by the Local Ethics Committee (H-B-2008-093), and the Danish Data Protection Agency (2015-41-3696). Both parents gave written informed consent before enrolment.

### Primary Exposure: Maternal Antibiotics during Pregnancy

Detailed information on maternal antibiotic use during pregnancy and 1 year after birth was collected prospectively from The Danish National Prescription Registry,<sup>19</sup> which records all prescription drugs purchased at Danish pharmacies, and linked with the recipient's unique personal identification number assigned by the Danish Civil Registration System.<sup>20</sup> Intake of collected medication was validated by interviews with participants. Treatments administered in hospitals or abroad were obtained through the interviews. Oral antibiotic use during pregnancy and in the first year after birth was analyzed as a dichotomized variable (yes/no), and for the pregnancy exposure also as categorized by the most likely treatment indication based on Anatomical Therapeutic Chemical code; respiratory tract infection (RTI) antibiotics (J01CAxx excl. J01CA08, J01CExx, J01FAxx, J01CRxx), and urinary tract infection (UTI) antibiotics (J01CA08, J01EBxx, J01XExx). Other antibiotics, which could not be categorized into one of these groups, were excluded owing to low numbers. Analyses were further stratified by treatment trimester; first trimester was defined as the first 14 weeks of gestation, second trimester as the 15th-26th weeks of gestation, third trimester as 27th week of gestation until birth. Numbers of treatments were analyzed as 0, 1, or 2 or more treatments to investigate possible dose-response effects.

### OM

All episodes of OM were registered in a structured daily symptom diary from birth to 3 years of age. Children with >90% valid diary information during the first 3 years of life were included in the analyses. An episode was defined as 1 or more concurrent days of parental registration of OM and the first day registered in the child's first episode was used in the survival analysis. OM diagnoses were verified by interviews at clinic visits and held up against antibiotic treatments with information from registers. The children were not seen in our research clinic with acute ear infections, but diagnosed by either an ear-nose-throat specialist or their general practitioner. The OM diagnosis, therefore, corresponds with doctor-diagnosed acute episodes of middle ear infection.

### VT

Information on all VT insertions in the first 3 years of life were extracted from 2 national registries: The Danish National Patient Registry using the International Classification of Diseases 10th revision code KDCA20 for all procedures performed at hos-

pitals, and The Danish National Health Service Registry using procedure code 3009 for all procedures performed in community otorhinolaryngology practices.<sup>21,22</sup> The date of the first VT insertion was used in the survival analysis.

### Covariates

Information regarding maternal asthma (doctor diagnosed), any maternal smoking during pregnancy (yes/no), older siblings in the household (defined as both biological and half siblings, with primary address in the home of the child), maternal age, maternal educational level (low [elementary school or college graduate], medium [tradesman or medium length], high [university]) and household income (low [<50 000 Euro], medium [50 000-110 000 Euro]), high [>110 000 Euro]) was obtained by personal interview at the 1-week clinical visit in the COPSAC research unit. Information regarding maternal and paternal history of middle ear disease was obtained from interviews at 3 years of age.

### Statistical Analyses

Baseline characteristics describing women with antibiotic use in pregnancy were analyzed by the  $\chi^2$  test for dichotomized variables. Normally distributed continuous variables were tested using Student *t* test. Variables not normally distributed were analyzed using Wilcoxon rank-sum test. The effect of maternal antibiotic use on age at first OM episode or VT insertion was quantified in terms of hazard ratios by Cox proportional hazards regression. The children were retained in the analysis from birth until age of event or 3 years of age, whichever came first. Possible confounders were chosen from results based on factors influencing maternal intake of antibiotics during pregnancy (Table I; available at [www.jpeds.com](http://www.jpeds.com)). Additionally, we also adjusted for presence of older siblings and family history of middle ear disease a priori, because these factors are known to affect the risk of OM and VTs.<sup>13,23,24</sup> The stratified analyses were also performed using Cox proportional hazard regression. No interaction was calculated. A significance level of 5% was used in all analyses. SAS version 9.4 for Windows (SAS Institute, Cary, North Carolina) was used for all data analysis.

## Results

Information on VT insertions was obtained from registries and available for all 700 children in the cohort, and information on maternal antibiotic intake during pregnancy was available for 699 children. The prevalence of any maternal antibiotic use during pregnancy was 37% (n = 256). In the first year after birth, 41% of the mothers (n = 283) were treated with antibiotics. The incidence of VT insertions before 3 years of age was 29% (n = 205). A total of 73% of the children (n = 514) had full follow-up and >90% valid diary information in the first 3 years of life and was included in the analyses of OM; 67% (n = 346) had  $\geq 1$  episode of OM in this period. We compared the children with adequate diary information with those who did not participate in the OM analysis and found that only maternal smoking during pregnancy was different significantly between these groups. There were fewer non-Caucasians,

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