J Antimicrob Chemother 2022; **77**: 1461–1467
https://doi.org/10.1093/jac/dkac053 Advance Access publication 2 March 2022

Journal of Antimicrobial Chemotherapy

Antibiotic use during pregnancy and the risk of preterm birth: a population-based Swedish cohort study

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Received 1 October 2021; accepted 28 January 2022

Objectives: To assess the impact of gestational antibiotics on the risk of preterm birth, since a healthy maternal microbiome may be protective.

Methods: Population-based cohort study including all first pregnancies in Sweden (2006–16). The association between gestational and recent pre-conception systemic antibiotics and preterm birth was assessed by multivariable logistic regression presented as ORs and 95% CIs, adjusted for comorbidities (hypo- and hyperthyroidism, hypertension, or diabetes mellitus pre-gestation), trimester, antibiotic class and treatment duration.

Results: Compared with non-users, antibiotic exposure was associated with increased risks of preterm birth in mothers with comorbidities (OR = 1.32, 95% CI 1.18–1.48) and without (OR = 1.09, 95% CI 1.06–1.13). Pre-conception use showed no association, while risk was increased for first and second trimester use and decreased for third trimester use. The increased risks were seen for the following antibiotic groups in mothers without and with comorbidities, respectively: macrolides, lincosamides and streptogramins (OR = 1.63, 95% CI 1.45–1.83; OR = 2.48, 95% CI 1.72–3.56); quinolones (OR = 1.60, 95% CI 1.32–1.94; OR = 2.11, 95% CI 1.12–4.03); non-penicillin β-lactams (OR = 1.15, 95% CI 1.07–1.24; OR = 1.39, 95% CI 1.07–1.83); other antibacterials (OR = 1.09, 95% CI 1.03–1.14; 1.38, 95% CI 1.16–1.63); and penicillins (OR = 1.04, 95% CI 1.01–1.08; 1.23, 95% CI 1.09–1.40). Antibiotic indications were not available, which could also affect preterm birth.

Conclusions: Antibiotic use during pregnancy was associated with an increased risk of preterm birth, especially in mothers with chronic diseases.

Introduction

Preterm birth is a major global health issue with an increasing prevalence.[1] Every year, an estimated 15 million babies are born prematurely with many of these children facing long-term health problems.[1,2] In fact, it is the second leading cause of fatality for children under 5 years old worldwide.[3] Preterm birth occurs spontaneously in up to 75%, or is induced.[3,4] Although the causes have been intensively investigated, they remain unclear for most cases.[3] Established predictors include history of preterm birth, twin pregnancies, known maternal anatomical or medical problems (short cervical length and a raised cervical–vaginal foetal fibronectin concentration),[4] symptomatic infections and other immunologically mediated processes.[4] In addition, a growing amount of evidence suggests that dysbiosis, an 'abnormal' gut and/or vaginal microbiome, may be associated with preterm birth.[5–7]

One of the common causes of dysbiosis is the exposure to different drugs, including antibiotics.[8,9] Therefore, as many studies have shown a link between antibiotic exposure during the gestational period and elevated risk of pregnancy complications (e.g. organ-specific malformations, prolonged pregnancy, spontaneous abortion), more efforts are needed to understand the role of the microbiome and its modulators in these pathologies.[10–12] This is of particular interest since, clinically, antibiotics have also been administered with the aim to reduce the risk of

preterm birth both for symptomatic and asymptomatic infections such as bacterial vaginosis.[13–15]

The aim of this study was to investigate the association between the timing and duration of use of antibiotics, in general and by antibiotic type, during pregnancy and the risk of preterm birth in a large nationwide and population-based cohort in Sweden.

Materials and methods

We performed a retrospective cohort study based on prospectively collected registry data, as described earlier.[16] The data were extracted from several Swedish nationwide health databases, including The Swedish Medical Birth Registry (established in 1973),[17] The Swedish Prescribed Drug Registry (established July 2005)[18] and The Swedish Patient Register (full nationwide coverage since 1987).[19] These high-quality registries cover the entire Swedish population, and are linked together by a unique personal identity number. This study included all women with complete records on prescribed drug exposure during pregnancy and the 3 months before conception. Because previous preterm birth is an established risk factor for consequent preterm deliveries, only first liveborn singleton births in Sweden from July 2006 to December 2016 were taken into consideration to have a more homogenous population. An additional analysis including all births was performed to assess the robustness of our findings and to establish whether the impact of antibiotics on preterm birth differed between the first and following pregnancies, incorporating history of preterm birth and birth order of the current pregnancy. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Regional Ethics Committee in Stockholm (2017/2423-31). Informed consent was not required because of the registry-based nature of the data.

Outcome

Preterm birth was defined as liveborn babies with a gestational length of less than 37 completed weeks [as dated at ultrasound, from embryo transfer or last menstrual period (LMP)]. This includes both spontaneous and induced preterm birth. The start day of the LMP was calculated by subtracting gestational age from the day of birth (as the birth date was given in year/month format due to privacy regulations, the day of birth was set as the 15th in all the observations).[16]

Study exposure

Systemic antibiotic use is defined based on the Anatomical Therapeutic Chemical (ATC) classification system of the WHO.[20] Antibacterials for systemic use (J01) consisting of 11 classes were studied, including: tetracyclines (J01A), amphenicols (J01B), β-lactam antibacterials, penicillins (J01C), other β-lactam antibacterials (J01D), sulphonamides and trimethoprim (J01E), macrolides, lincosamides and streptogramins (J01F), aminoglycoside antibacterials (J01G), quinolone antibacterials (J01M), combinations of antibacterials (J01R) and other antibacterials including among others imidazole derivates and nitrofurans (J01X). Note that as J01X also includes imidazole derivates, nitroimidazole derivates (P01AB) were included in the same category, and that indications of use are not recorded in the Prescribed Drug Registry.

Exposure to investigated antibiotics was defined as at least one prescription to the pregnant woman between conception and delivery. The utilization units for drugs were number of prescriptions and estimated duration of treatment, based on the number of defined daily doses (DDDs) in dispensed packages given that one DDD corresponds to 1 day of treatment for the standard indication in adults.[20]

To assess dosage and duration of each class of antibiotics, we assessed the sum of all prescriptions and the estimated number of days exposed during the entire pregnancy based on the prescribed DDD per package. Sub-analyses were conducted on antibiotic use during each trimester of the pregnancy. The first trimester was defined as from LMP to 97 days of gestation, the second trimester 98–202 days and the third trimester 203 days until delivery. In addition, to investigate long-term effect, exposure to maternal antibiotics during 3 months pre-conception was also be examined. Individuals using antibiotics during multiple time periods (trimesters and preconception) were excluded from these analyses.

Covariates

Other covariates considered in the analysis included maternal characteristics [maternal age at childbirth, maternal BMI at early pregnancy (before 12 weeks), mother's country of birth], lifestyle factors (tobacco consumption at any time during pregnancy, including smoking and snuff or smokeless tobacco), common pre-pregnancy maternal chronic comorbidities (hypo- and hyperthyroidism, hypertension, or diabetes mellitus) and birth history (history of stillbirth or miscarriage) as retrieved from the Medical Birth Registry and Patient Registry. History of preterm birth was only included in the additional analyses. Exposure to specific treatments {[ATC: A02B]: gastric acid inhibitors [proton-pump inhibitors (PPIs), H2-receptor antagonists (H2RA)], and *Helicobacter pylori* eradication} was also considered since these drugs may affect the microbiome.[8]

Statistical analysis

Multivariable logistic regression was used to assess the risk of preterm birth associated with antibiotic exposure during first pregnancy while adjusting for other covariates, presented as adjusted ORs with 95% CIs.

The starting model included the study exposure and all covariates (Model 1). Backward model selection was based on the Wald statistic with a cut-off value for alpha of 0.05. The fit of the reduced model was compared with the previous model using likelihood ratio test to confirm the insignificance of a removed predictor. If the elimination of one predictor led to more than 20% adjustment in coefficient magnitude of another variable, that predictor was added back.[21] After obtaining a final main-effects model (Model 2), we proceeded to add all interactions that deemed clinically important (Model 3) and re-applied the procedure above to build the final model (Model M). Only insignificant interactions were removed in this process. Because our objective was to investigate the association between antibiotic exposure and preterm birth, the variables corresponding to the study exposure were kept in the model regardless of significance.

Two additional analyses were done to assess the robustness of the findings. The first excluded women who were also exposed to local (vaginal) gynaecological anti-infectives and antiseptics ([G01] group), since this antibiotic group may affect the maternal vaginal microbiome.

The second included all pregnancies instead of restricting analyses to the first pregnancy. For this second additional analysis, we first added two variables (history of preterm birth and birth order of current pregnancy) to Model 3. Generalized Estimating Equations were used for these correlated data and an 'independence' working correlation was chosen because it resulted in the lowest QIC and the least deviation between model-based versus robust standard errors.[22] After that, a parsimonious model was built following the same procedure as in the case of ordinary logistic regression but based on the covariate's *P* value of its Wald test and model QIC. The final model was the one with the lowest QIC.

All analyses were conducted with R version 3.6.1. For missing values, an extra category was created since otherwise a too large proportion of the cohort needed to be excluded (7% missingness for BMI) and imputing missing values was not computationally feasible due to the cohorts' size.

Results

Descriptive characteristics

The cohort included 483706 alive first pregnancies during 2006–16, of which 5.8% were preterm deliveries (Table 1). Overall, 20.5% of the mothers were exposed to antibiotics during their gestation period. Antibiotic users, as a group, were younger (69.2% aged less than 31 years old) and included more tobacco users (26.1%) compared with non-users (20.5%). Antibiotic users and non-users were similar for other characteristics.

Use of antibiotics and the risk of preterm birth

Overall, 22.4% of mothers delivering preterm used antibiotics (at any time during their pregnancy) compared with 20.3% of term deliveries. Interaction was present between antibiotic use and maternal comorbidities, and the ORs of preterm birth are presented separately in Table 2. Compared with non-users, antibiotic use was associated with an increased risk of preterm birth in mothers with comorbidities (OR = 1.32, 95% CI 1.18–1.48); yet also increased in mothers without comorbidities (OR = 1.09, 95% CI 1.06–1.13).

Almost all antibiotic classes showed increased risks except for tetracyclines, sulphonamides and trimethoprim. Due to convergence issues related to data sparseness, the aminoglycosides were not studied further. The largest effect was seen for macrolides, lincosamides and streptogramins (OR = 1.63, 95% CI 1.45–1.83), quinolones (OR = 1.60, 95% CI 1.32–1.94) and non-penicillin β-lactams (OR = 1.15, 95% CI 1.07–1.24) among mothers without comorbidities. The figures among mothers with comorbidities were 2.48 (95% CI 1.72–3.56), 2.11 (95% CI 1.12–4.03) and 1.39 (95% CI 1.07–1.83), respectively.

Trimester of pregnancy

There was no association between the use of antibiotics 3 months before pregnancy and preterm birth (Table 3). Antibiotic exposure within the first and second trimester was associated with an increased risk of preterm birth. For mothers without comorbidities, this corresponded to OR = 1.08 (95% CI 1.02–1.14) (first trimester) and OR = 1.33 (95% CI 1.26–1.40) (second trimester). For mothers with comorbidities, this corresponded to OR = 1.43 (95% CI 1.16–1.75) (first trimester) and OR = 1.53 (95% CI 1.26–1.85) (second trimester). However, antibiotic use during the third trimester showed a decreased risk in mothers without (OR 0.82, 95% CI 0.77–0.88) and with comorbidities (OR 0.80, 95% CI 0.63–1.03).

Dose–response association

The results suggested a dose-dependent relationship between antibiotic use and preterm birth (Table 4). Among mothers without comorbidities, each additional prescription of antibiotics during pregnancy increased the risk of preterm birth (OR = 1.040, 95% CI 1.024–1.057 and OR = 1.139, 95% CI 1.088–1.192 in mothers without and with comorbidities). Similar findings were found for each additional day using antibiotics (OR = 1.003, 95% CI 1.002–1.004 and OR = 1.004, 95% CI 1.001–1.007 in mothers without and with comorbidities) (Table 4).

Table 1. Prevalence of exposure to antibiotics with regards to maternal characteristics in all singleton pregnancies in Sweden (2006–16)

	Antibiotic use		No Antibiotic use		Total	
Characteristics	*N*	%	*N*	%	*N*	%
Total	98963	20.5	384743	79.5	483706	100.0
Maternal age, years						
≤25	34578	35.0	107381	27.9	141959	29.3
26–30	33870	34.2	146917	38.2	180787	37.4
≥31	30515	30.8	130445	33.9	160960	33.3
Maternal BMI, kg/m^2						
<18.5	3109	3.2	10648	2.7	13757	2.8
18.5–24.9	56527	57.1	230877	60.0	287404	59.4
25.0–29.9	21324	21.5	81499	21.2	102823	21.3
≥30.0	11085	11.2	35611	9.3	46696	9.7
Data missing	6918	7.0	26108	6.8	33026	6.8
Tobacco consumption						
Yes	25757	26.1	78914	20.5	104671	21.6
No	69117	69.8	289920	75.4	359037	74.2
Data missing	4089	4.1	15909	4.1	19998	4.1
Chronic comorbidities[a]						
Yes	4015	4.1	11706	3.0	15721	3.3
No	94948	95.9	373037	97.0	467985	96.7
Exposure to other drugs[b]						
Yes	5820	5.9	12210	3.2	18030	3.7
No	93143	94.1	372533	96.8	465676	96.3
Mother's country of birth						
Nordic	75836	76.7	299209	77.8	375045	77.5
Non-Nordic	22988	23.2	84716	22.0	107704	22.3
Data missing	139	0.1	818	0.2	957	0.2
History of Stillbirth						
Yes	132	0.1	372	0.1	504	0.1
None recorded	98831	99.9	384371	99.9	483202	99.9
History of Miscarriage						
Yes	16537	16.7	58841	15.3	75378	15.6
None recorded	82426	83.3	325902	84.7	408328	84.4

[a]Comorbidities defined as at least one recorded pre-gestation diagnosis of hypothyroidism, hyperthyroidism, hypertension and/or diabetes mellitus.
[b]Other drugs defined as at least on dispensed prescription of gastric acid inhibitors [proton-pump inhibitors (PPIs), H2-receptor antagonists (H2RA)] and/or *Helicobacter pylori* eradication [A02B].

Additional analyses

Both additional analyses—excluding gynaecological antibiotic use and including later pregnancies—provided similar results that antibiotic exposure during pregnancy was associated with an increased risk of preterm, as shown in Table 5.

Discussion

This large Swedish population-based study on all first singleton pregnancies (2006–16) showed a higher risk of preterm birth among antibiotic users compared with non-users, although causality cannot be established. The effect was more apparent

Table 2. Association between antibiotic exposure during pregnancy and preterm birth, using multivariable regression expressed as ORs and 95% CIs using all non-users as comparison group

	Number of users	Number of preterm births (%)	Median number of prescriptions (IQR)	Median number of days exposed (IQR)	In mothers *without* selected chronic comorbidities	In mothers *with* selected chronic comorbidities
Aminoglycosides	13	5 (38.5)	1.5 (1)	56.0 (61.5)	–	–
β-lactam, penicillins	69540	4246 (6.1)	1.0 (0)	10.0 (10.0)	1.04 (1.01–1.08)	1.23 (1.09–1.40)
β-lactam, others	12360	833 (6.7)	1.0 (0)	5.0 (6.5)	1.15 (1.07–1.24)	1.39 (1.07–1.83)
Macrolides, lincosamides and streptogramins	3767	364 (9.7)	1.0 (0)	5.0 (3.0)	1.63 (1.45–1.83)	2.48 (1.72–3.56)
Quinolones	1365	126 (9.2)	1.0 (0)	8.0 (5.0)	1.60 (1.32–1.94)	2.11 (1.12–4.03)
Sulphonamides and trimethoprim	1788	118 (6.6)	1.0 (0)	5.6 (1.9)	1.11 (0.91–1.35)	1.66 (0.91–3.03)
Tetracyclines	2984	161 (5.4)	1.0 (0)	10.0 (20.0)	0.92 (0.78–1.09)	0.84 (0.43–1.61)
Other antibacterials	29884	1908 (6.4)	1.0 (0)	6.0 (3.8)	1.09 (1.03–1.14)	1.38 (1.16–1.63)
Overall	98963	6229 (6.3)	1.0 (1)	10.0 (10.0)	1.09 (1.06–1.13)	1.32 (1.18–1.48)

Chronic comorbidities defined as at least one recorded pre-gestation diagnosis of hypothyroidism, hyperthyroidism, hypertension and/or diabetes mellitus.

All analyses are adjusted for chronic comorbidities, maternal age, BMI, tobacco consumption, exposure to other drugs, mother's country of birth, history of stillbirth and history of miscarriages.

in mothers with at least one comorbidity (32% increase) than in women without (9% increase), with similar findings among most analysed antibiotic classes, with the highest risks for macrolides and quinolones. There was a dose–response effect, with more antibiotic intake being associated with higher risks, yet the actual intake may have been overestimated because it is based on the total prescribed packages. When assessed per gestational period, an apparent protective effect was noted for exclusive exposure during the third trimester, which may partially be due to selection bias (some preterm babies already born). Notably, antibiotic use before pregnancy was not associated with increased risk of preterm birth.

Strengths of this study are the large population, valid data sources, and possibility to explore different potential biases and confounders. Since all eligible women were included, there was no risk of selection bias, and therefore our results should be generalizable to other singleton pregnancy cohorts with similar patterns of antibiotic consumption. Non-singleton pregnancies were excluded because of an *a priori* higher risk of preterm birth. The prevalence and types of antibiotics used in this cohort are comparable to European estimates; with penicillins most commonly used.[23–27] Recall bias is often a problem in studies on exposures during pregnancy. However, since antibiotics are only available on prescription, and the Swedish Prescribed Drug Registry is virtually complete for outpatient use,[18] the risk of misclassification based on exposure should be limited, although in-hospital antibiotic use was not included in the Swedish Prescribed Drug Registry. Yet, compliance to the prescribed treatment cannot be assessed and may be lower during pregnancy than otherwise because of perceived risks. Yet, we do know that the prescriptions have been dispensed in the pharmacy. We did plan to include common comorbidities during pregnancy as confounder in our models, but since an interaction was found with antibiotic consumption, we only presented stratified results based on presence or absence of these comorbidities. As could be expected, antibiotic use is particularly associated with an increased risk of preterm birth in those with comorbidities, which may be risk factors for preterm birth by itself (and may need further exploration in the future). Yet, a 9% increase was also noted in women without these comorbidities. We also assessed this association in later pregnancies and found similar results. After exclusion of women exposed to gynaecological antibiotics and antiseptics, the results remained largely unchanged.

Our study has some limitations. We could not distinguish between spontaneous and induced preterm birth, yet it has been suggested that both subtypes have overlapping aetiology.[28,29] Unfortunately, the underlying mechanism of this antibiotic use

Table 3. Association between antibiotic exposure per gestational trimester and preterm birth (exclusive use in each trimester), using all non-users as reference and expressed as ORs and 95% CIs

	In mothers *without* selected chronic comorbidities	In mothers *with* selected chronic comorbidities
Three months pre-pregnancy	1.01 (0.95–1.07)	1.02 (0.81–1.27)
First trimester	1.08 (1.02–1.14)	1.43 (1.16–1.75)
Second trimester	1.33 (1.26–1.40)	1.53 (1.26–1.85)
Third trimester	0.82 (0.77–0.88)	0.80 (0.63–1.03)

All analyses are adjusted for chronic comorbidities, maternal age, BMI, tobacco consumption, exposure to other drugs, mother's country of birth, history of stillbirth and history of miscarriages.

Table 4. Dose–response association between antibiotic exposure during pregnancy and preterm birth as calculated by means of multivariable logistic regression, expressed as ORs and 95% CIs

	In mothers *without* selected chronic comorbidities	In mothers *with* selected chronic comorbidities
Number of prescriptions		
For each additional prescription (continuous)	1.040 (1.024–1.057)	1.139 (1.088–1.192)
Per category (reference: non-users)		
One prescription	1.096 (1.058–1.136)	1.219 (1.067–1.393)
Two prescriptions	1.065 (1.001–1.133)	1.526 (1.242–1.875)
Three or more prescriptions	1.120 (1.031–1.216)	1.511 (1.192–1.915)
Number of days exposed		
For each additional day exposed (continuous)	1.003 (1.002–1.004)	1.004 (1.001–1.007)
Per category (reference: non-users)		
1–4 days	1.121 (1.055–1.191)	1.246 (0.990–1.570)
5–9 days	1.147 (1.089–1.208)	1.302 (1.072–1.581)
10–14 days	1.051 (0.986–1.120)	1.375 (1.113–1.697)
15 days or more	1.054 (1.003–1.108)	1.346 (1.140–1.589)

All analyses are adjusted for chronic comorbidities, maternal age, BMI, tobacco consumption, exposure to other drugs, mother's country of birth, history of stillbirth and history of miscarriages.

and preterm birth association cannot be assessed and confounding by indication, e.g. by urinary tract infections,[30] may play a role. Indication of drug use is not registered in relation to the prescription (and only specialist-outpatient diagnoses and hospital discharge diagnoses are available). However, we did assess different types of antibiotics, which showed similar patterns. Our initial hypothesis was that systemic antibiotics affect the microbiome during pregnancy, in the vagina and other body niches. Therefore, we did want to include all antibiotic use, independent of the indication—although we recognize that the indication itself could trigger preterm birth.[31–34] Yet, by only including outpatient antibiotics, some of the severe infections requiring hospitalizations with exclusive inpatient use were not included. Macrolides and lincosamides showed the strongest associations with preterm birth, yet can be prescribed for conditions linked to preterm birth, including bacterial vaginosis, *Ureaplasma* colonization or short cervix—despite potentially suboptimal treatment efficacy in reducing the preterm risk.[35–40] Some antibiotic groups like tetracyclines should always be avoided during pregnancy because of teratogenicity. In our complete cohort, approximately two-thirds of tetracyclines were given in the 3 months preconception, and one-third in the first trimester, with only 6% during later pregnancy.

We only included liveborn singleton pregnancies, because of the established higher risk of preterm birth for twin pregnancies; and the potentially different aetiology of stillbirth and need to censor follow-up time for those cases. The exclusion of pregnancies resulting in stillbirth could be discussed, since antibiotic exposure may affect the risk, and these pregnancies were at risk for our outcome, preterm birth, at the start. Yet, including those pregnancies is unlikely to have affected the results (only 0.3% of all deliveries in Sweden[17]).

While exposure during the first or second trimester of pregnancy showed an increased risk of preterm birth, antibiotics during the third trimester (starting at the 27th gestational week) were associated with a decrease in mothers without selected comorbidities. It was noted that, in this study, among preterm pregnancies, 5.5% were extremely preterm (gestational age <28 weeks), 9.7% were very preterm (gestational age 28 to <32 weeks) and 84.9% were moderate to late preterm (gestational age 32 to <37 weeks), so survival bias may not explain the apparent protective effect towards the end of the pregnancy entirely. Yet, if antibiotics are given late during the third trimester, they may not have had time to have an impact on the risk of preterm birth. As infections may be a trigger for preterm birth, the use of (some) antibiotics may truly be protective during the third trimester; or at least less harmful than the infection itself given that the treatment is initiated before inflammatory reactions and tissue damage occur.[15,41] Yet, it has been postulated that very early spontaneous preterm birth may be more likely to be of infectious aetiology than later preterm birth.[15]

The findings from this study add more weight to recent evidence on the role of the microbiome and the risk of preterm birth, stressing the need to re-consider the risk–benefit of antibiotics in pregnant women. There is increasing evidence that bacterial vaginosis, or vaginal dysbiosis is linked to the risk of preterm birth,[37] yet this does not imply antibiotic treatment will reduce this risk; a meta-analysis from 2007 looking explicitly at the use of prophylactic antibiotics, to reduce the risk of preterm birth, in 17 trials concluded antibiotics did not lower the risk of preterm birth (relative risk 1.03, 95% CI 0.86–1.24).[42] Another meta-analysis looking at quinolone use during the first trimester (four observational studies, 1678 exposed women) concluded there was no increased risk of preterm birth, although the pooled OR was 1.10%, yet with broad 95% CI (0.83–1.48).[43] Another meta-analysis on quinolones published in the same year concluded that the risk of preterm birth was decreased (OR 0.97, 95% CI 0.75–1.24 based on four studies and 771 exposed women, of which only 1 overlapped with the other meta-analysis).[44] Another meta-analysis from 2008 on second-trimester use of

Table 5. Association between antibiotic exposure during pregnancy and preterm birth based on different inclusion criteria, as calculated by multivariable logistic regression and expressed as ORs and 95% CIs using non-users as reference

	Number of pregnancies	In mothers *without* selected chronic comorbidities	In mothers *with* selected chronic comorbidities
All first pregnancies (main analysis)	483706	1.09 (1.06–1.13)	1.32 (1.18–1.48)
Excluding women using gynaecological antibiotics	466519	1.09 (1.05–1.12)	1.31 (1.16–1.46)
Including all pregnancies (not restricted to first pregnancy)[a]	789360	1.12 (1.09–1.15)	1.31 (1.20–1.43)

All analyses are adjusted for chronic comorbidities, maternal age, BMI, tobacco consumption, exposure to other drugs, mother's country of birth, history of stillbirth and history of miscarriages.
[a]Additional adjustment for birth order and history of preterm birth.

antibiotics based on three trials concluded that macrolides and clindamycin were associated with a lower risk, yet metronidazole with a greater risk of preterm birth (OR 1.31, 95% CI 1.08–1.58) in high-risk populations.[45]

It appears that the microbiome composition and especially specific pathogens causing symptomatic infections may have an impact on the risk of preterm birth. Yet, antibiotic treatment by itself may also increase the risk of preterm birth potentially related to microbiome changes. Careful evaluation of cost–benefits for the individual pregnant woman seems required when considering antibiotic treatment; and some antibiotic groups like tetracyclines should always be avoided during pregnancy because of teratogenicity (yet could have been used in this cohort in the 3 months prior pregnancy or before the woman was aware of her pregnancy).

In conclusion, this study shows antibiotic use during pregnancy, particularly during the first and second trimester, was associated with an increased risk of preterm birth, with a potential decreased risk in the third trimester.

Funding

This study was supported by internal funding. R.B. was funded as a postdoctoral researcher by the Research Foundation—Flanders (FWO: 2019-2021, 12I6319N). R.F. was funded by Becas Chile, HKH Kronprinsessan Lovisas förening för barnasjukvård och Stiftelsen Axel Tielmans minnesfond Lovisas.

Transparency declarations

None to declare.

References

1 Walani SR. Global burden of preterm birth. *Int J Gynaecol Obstet* 2020; **150**: 31–3.

2 Liu L, Oza S, Hogan D *et al*. Global, regional, and national causes of under-5 mortality in 2000-15: an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet* 2016; **388**: 3027–35.

3 Blencowe H, Cousens S, Chou D *et al*. Born too soon: the global epidemiology of 15 million preterm births. *Reprod Health* 2013; **10** Suppl 1: S2.

4 Goldenberg RL, Culhane JF, Iams JD *et al*. Epidemiology and causes of preterm birth. *Lancet* 2008; **371**: 75–84.

5 Staude B, Oehmke F, Lauer T *et al*. The microbiome and preterm birth: A change in paradigm with profound implications for pathophysiologic concepts and novel therapeutic strategies. *Biomed Res Int* 2018; **2018**: 7218187.

6 Fettweis JM, Serrano MG, Brooks JP *et al*. The vaginal microbiome and preterm birth. *Nat Med* 2019; **25**: 1012–21.

7 Côté N, Pasquier J-C. [Spontaneous preterm birth and the maternal microbiome]. *Med Sci (Paris)* 2018; **34**: 799–805.

8 Brusselaers N. Prescribed drugs and the microbiome. *Gastroenterol Clin North Am* 2019; **48**: 331–42.

9 Vich Vila A, Imhann F, Collij V *et al*. Gut microbiota composition and functional changes in inflammatory bowel disease and irritable bowel syndrome. *Sci Transl Med* 2018; **10**: eaap8914.

10 Muanda FT, Sheehy O, Bérard A. Use of antibiotics during pregnancy and the risk of major congenital malformations: a population based cohort study. *Br J Clin Pharmacol* 2017; **83**: 2557–71.

11 Muanda FT, Sheehy O, Bérard A. Use of antibiotics during pregnancy and risk of spontaneous abortion. *CMAJ* 2017; **189**: E625–33.

12 Shiffman RL. Continuous low-dose antibiotics and cerclage for recurrent second-trimester pregnancy loss. *J Reprod Med* 2000; **45**: 323–6.

13 Carey JC, Klebanoff MA, Hauth JC *et al*. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med* 2000; **342**: 534–40.

14 Klebanoff MA, Carey JC, Hauth JC *et al*. Failure of metronidazole to prevent preterm delivery among pregnant women with asymptomatic *Trichomonas vaginalis* infection. *N Engl J Med* 2001; **345**: 487–93.

15 Lamont RF. Can antibiotics prevent preterm birth—the pro and con debate. *BJOG* 2005; **112** Suppl 1: 67–73.

16 Fornes R, Simin J, Nguyen MH *et al*. Pregnancy, perinatal and childhood outcomes in women with and without Polycystic Ovary Syndrome and metformin during pregnancy: a nationwide population-based study. *Reprod Biol Endocrinol* 2022; **20**: 30.

17 The Swedish Medical Birth Registry - Statistics Sweden. https://www.socialstyrelsen.se/statistik-och-data/.

18 Wettermark B, Hammar N, Fored CM *et al*. The new Swedish Prescribed Drug Register—opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* 2007; **16**: 726–35.

19 Ludvigsson JF, Andersson E, Ekbom A *et al*. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011; **11**: 450.

20 WHO – Collaborating Centre for Drug Statistics Methodology. https://www.whocc.no/2020.

21 Hosmer D Jr, Lemeshow S, Sturdivant R. *Applied Logistic Regression*. Vol. 398. John Wiley & Sons, Inc., 2013.

22 Pan W. Akaike's information criterion in generalized estimating equations. *Biometrics* 2001; **57**: 120–5.

23 Stephansson O, Granath F, Svensson T *et al*. Drug use during pregnancy in Sweden - assessed by the Prescribed Drug Register and the Medical Birth Register. *Clin Epidemiol* 2011; **3**: 43–50.

24 Adriaenssens N, Coenen S, Versporten A *et al*. European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe (1997-2009). *J Antimicrob Chemother* 2011; **66** Suppl 6: vi13–12.

25 Bookstaver PB, Bland CM, Griffin B *et al*. A review of antibiotic use in pregnancy. *Pharmacotherapy* 2015; **35**: 1052–62.

26 Bruyndonckx R, Hens N, Aerts M *et al*. Measuring trends of outpatient antibiotic use in Europe: jointly modelling longitudinal data in defined daily doses and packages. *J Antimicrob Chemother* 2014; **69**: 1981–6.

27 Bruyndonckx R, Hoxha A, Quinten C *et al*. Change-points in antibiotic consumption in the community, European Union/European Economic Area, 1997-2017. *J Antimicrob Chemother* 2021; **76** Suppl 2: ii68–78.

28 Ananth CV, Vintzileos AM. Epidemiology of preterm birth and its clinical subtypes. *J Matern Fetal Neonatal Med* 2006; **19**: 773–82.

29 McElrath TF, Hecht JL, Dammann O *et al*. Pregnancy disorders that lead to delivery before the 28th week of gestation: an epidemiologic approach to classification. *Am J Epidemiol* 2008; **168**: 980–9.

30 Werter DE, Schneeberger C, Mol BWJ *et al*. The risk of preterm birth in low risk pregnant women with urinary tract infections. *Am J Perinatol* 2021; https://doi.org/10.1055/s-0041-1739289.

31 Pararas MV, Skevaki CL, Kafetzis DA. Preterm birth due to maternal infection: Causative pathogens and modes of prevention. *Eur J Clin Microbiol Infect Dis* 2006; **25**: 562–9.

32 Hillier SL, Nugent RP, Eschenbach DA *et al*. Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. The Vaginal Infections and Prematurity Study Group. *N Engl J Med* 1995; **333**: 1737–42.

33 Kurki T, Sivonen A, Renkonen OV *et al*. Bacterial vaginosis in early pregnancy and pregnancy outcome. *Obstet Gynecol* 1992; **80**: 173–7.

34 Andrews WW, Hauth JC, Goldenberg RL. Infection and preterm birth. *Am J Perinatol* 2000; **17**: 357–65.

35 Reboucas KF, Eleuterio J Jr, Peixoto RC *et al*. Treatment of bacterial vaginosis before 28 weeks of pregnancy to reduce the incidence of preterm labor. *Int J Gynaecol Obstet* 2019; **146**: 271–6.

36 Peelen MJ, Luef BM, Lamont RF *et al*. The influence of the vaginal microbiota on preterm birth: A systematic review and recommendations for a minimum dataset for future research. *Placenta* 2019; **79**: 30–9.

37 Kosti I, Lyalina S, Pollard KS *et al*. Meta-analysis of vaginal microbiome data provides new insights into preterm birth. *Front Microbiol* 2020; **11**: 476.

38 McDonald HM, Brocklehurst P, Gordon A. Antibiotics for treating bacterial vaginosis in pregnancy. *Cochrane Database Syst Rev* 2007: CD000262.

39 Motomura K, Romero R, Xu Y *et al*. Intra-amniotic infection with Ureaplasma parvum causes preterm birth and neonatal mortality that are prevented by treatment with clarithromycin. *mBio* 2020; **11**: e00797-20.

40 Kunpalin Y, Burul G, Greenwold N *et al*. Factors associated with preterm birth in women undergoing cervical cerclage. *Eur J Obstet Gynecol Reprod Biol* 2020; **251**: 141–5.

41 Bowes WA. The role of antibiotics in the prevention of preterm birth. *F1000 Med Rep* 2009; **1**: 22.

42 Simcox R, Sin W-TA, Seed PT *et al*. Prophylactic antibiotics for the prevention of preterm birth in women at risk: a meta-analysis. *Aust N Z J Obstet Gynaecol* 2007; **47**: 368–77.

43 Ziv A, Masarwa R, Perlman A *et al*. Pregnancy outcomes following exposure to quinolone antibiotics – a systematic-review and meta-analysis. *Pharm Res* 2018; **35**: 109.

44 Yefet E, Schwartz N, Chazan B *et al*. The safety of quinolones and fluoroquinolones in pregnancy: a meta-analysis. *BJOG* 2018; **125**: 1069–76.

45 Morency A-M, Bujold E. The effect of second-trimester antibiotic therapy on the rate of preterm birth. *J Obstet Gynaecol Can* 2007; **29**: 35–44.