Thieme

# Antibiotic Use During Pregnancy and Childbirth: Prospective Observational Study on Prevalence, Indications, and Prescribing Patterns in a German Tertiary Center

## Einsatz von Antibiotika während Schwangerschaft und Geburt: Prospektive Beobachtungsstudie zu Prävalenz, Indikationen und Verschreibungsmustern in einem deutschen Perinatalzentrum

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## ABSTRACT

**Introduction** Antibiotics are powerful drugs to prevent and treat perinatal infections. Overuse of antibiotics leads to antibiotic resistance, has potential side effects and influences the maternal and neonatal microbiome.

**Patients and Methods** We performed a prospective observational study on the prevalence, indications, and prescribing patterns of antibiotics during pregnancy and childbirth. We included women who had given birth after 23 + 0 weeks of gestation at a single tertiary center in Germany from January 2020 to March 2021. Descriptive statistics and binomial regression were performed to analyze the factors influencing the prescription of antibiotics.

**Results** We included 522 postpartum women into our study. 337 (64.6 %) were exposed to antibiotics during pregnancy and/or childbirth. 115 women received antibiotics during pregnancy, 291 during birth. Most antibiotics during pregnancy were prescribed for urinary tract infections (UTIs) (56.0 %). Most prescriptions were issued by obstetrics and gynecology physicians (65.8 %), followed by hospitals (16.7 %) and family medicine physicians (8.8 %). Most antibiotics during childbirth were given for a cesarean section (64.3 %), followed by preterm rupture of membranes (41.2 %). 95.3 % of women who had a preterm birth were exposed to antibiotics. In logistic regression models, lower gestational age at birth, higher maternal body-mass-index and smoking were independently associated with antibiotic use during pregnancy and childbirth.

**Conclusion** We found a high rate of antibiotic exposure during pregnancy and childbirth. Our results imply an urgent need for antibiotic stewardship programs in perinatal medicine as well as further research on the effects of perinatal antibiotic exposure on microbiome development and childhood health.

## ZUSAMMENFASSUNG

**Einleitung** Antibiotika sind potente Medikamente, die verschrieben werden, um perinatale Infektionen zu verhindern oder zu behandeln. Der übermäßige Einsatz von Antibiotika führt zur Antibiotikaresistenz, ist potenziell mit Nebenwirkungen behaftet und hat zudem Auswirkungen auf das mütterliche und neonatale Mikrobiom.

**Patientinnen und Methoden** Wir führten eine prospektive Beobachtungsstudie durch, um die Prävalenz, die Indikationen und die Verschreibungsmuster für Antibiotika während der Schwangerschaft und der Geburt zu untersuchen. Eingeschlossen wurden Frauen, die nach 23 + 0 Schwangerschaftswochen zwischen Januar 2020 and März 2021 in einem deutschen universitären Perinatalzentrum Level I entbanden. Es wurden eine deskriptive statistische Analyse sowie binomiale Regressionsanalysen durchgeführt, um Faktoren, welche die Verschreibung von Antibiotika beeinflussen, zu identifizieren.

**Ergebnisse** Insgesamt wurden 522 Frauen nach der Entbindung eingeschlossen. 337 (64,6 %) erhielten Antibiotika während der Schwangerschaft und/oder der Geburt. 115 Frauen erhielten Antibiotika während der Schwangerschaft und 291 Frauen erhielten sie während der Geburt. Die meisten Antibiotika wurden während der Schwangerschaft zur Behandlung von Harnwegsinfektionen verschrieben (56,0 %). Die meisten Verschreibungen wurden von Frauenärzten ausgestellt (65,8 %), gefolgt von Krankenhäusern (16,7 %) und Hausärzten (8,8 %). Die meisten während der Geburt verabreichten Antibiotika wurden wegen eines Kaiserschnitts (64,3 %) verschrieben; an zweiter Stelle war die Verschreibung wegen vorzeitigen Blasensprungs (41,2 %). 95,3 % der Frauen, die eine Frühgeburt hatten, wurden mit Antibiotika behandelt. In den Regressionsmodellen war ein niedriges Gestationsalter bei der Entbindung, ein hoher mütterlicher Body-Mass-Index und Rauchen unabhängig voneinander mit dem Einsatz von Antibiotika während der Schwangerschaft und der Geburt assoziiert.

**Schlussfolgerung** Unsere Studie zeigt eine hohe Antibiotikaexposition von Frauen während Schwangerschaft und Geburt. Die Ergebnisse weisen darauf hin, dass ein Antibiotic-Stewardship-Programm in der Perinatalmedizin dringend nötig ist. Weitere Studien zu den Auswirkungen einer perinatalen Antibiotikaexposition auf die frühe Entwicklung des menschlichen Mikrobioms sowie auf die Gesundheit von Kindern werden benötigt.


## Introduction

Bacterial infections can cause serious perinatal morbidity and mortality of mothers and their infants [1, 2]. Antibiotics are powerful drugs to prevent and treat perinatal infections like chorioamnionitis or neonatal sepsis and to reduce preterm birth rates caused by infectious pathogens of the maternal genitourinary tract [3, 4].

On the contrary, antibiotics can have serious toxic and teratogenic side effects, or can cause maternal anaphylaxis and neonatal necrotizing enterocolitis (NEC) [5]. The total consumption of antibacterials for systemic use has significantly decreased over the last ten years in Europe [6]. This is attributed to a rising awareness for antimicrobial resistance and the implementation of antibiotic stewardship programs [7]. Antibiotic resistance is a global health threat increased by the widespread overuse of antibiotics. Antibiotic stewardship aims at promoting a sustainable and rational use of antimicrobials to ensure the accessibility of an effective antibiotic therapy for patients with bacterial infections [8]. Surveillance of antimicrobial use and resistance is an important tool to fight antimicrobial resistance on a national and international level [9]. In Germany, databases on antibiotic surveillance and antibiotic stewardship are organized by the Robert Koch Institute [10]. As of today, there is no specific national data on the use of antibiotics during pregnancy and childbirth.

The growing body of knowledge on the impact of perinatal antibiotic exposure on the neonatal microbiome is adding a new aspect to the discussion of antibiotic use in pregnancy and during early life. Apart from the proven benefits of prophylactic (e.g., for operative birth or group B streptococci) and therapeutic antibiotics (e.g., for chorioamnionitis or urinary tract infection) during pregnancy and childbirth [3, 11, 12, 13, 14], it has been shown that exposure to antibiotics in this critical phase can change the offspring's developing microbiota significantly [15, 16]. The initial colonization of the infant's gut at the beginning of life is influenced by several known factors like birth mode, breast-feeding versus formula feeding, microbial transfer by the mother, environment and early life antibiotic exposure [17]. Antibiotic resistance genes can already be found in the neonatal gut during the first days and weeks of life, making a vertical transmission highly probable [18, 19]. Exposure to antibiotics in pregnancy has been associated with a higher risk for childhood asthma, allergies and obesity [20, 21, 22]. In addition, antibiotics during infancy can influence childhood health including higher incidences for overweight and atopic diseases [23].

As current national data is lacking, we conducted a prospective observational study at a single tertiary center to evaluate the prevalence, indications, and prescribing patterns of antibiotics during pregnancy and childbirth in Germany.

## Patients and Methods

### Sample population

We performed a prospective observational study at a tertiary center in Germany from January 2020 to March 2021. We included postpartum women who had given birth at our hospital with a maternal age of at least 18 years. We excluded all stillbirths and births below 23 + 0 weeks of gestation. Postpartum women were contacted in three different ways to get consent for their study inclusion: Primarily, women were personally contacted on the maternity ward within the first days after birth. Due to entrance restrictions during the COVID-19 pandemic we additionally con-

tacted postpartum women at home after their discharge from the hospital either by phone or by mail to ask for their consent to participate in the study. Every woman provided written informed consent prior to inclusion. Approval by the local ethics committee for research in human subjects of the University of Lübeck has been granted (Reference number 20–063). Clinical data from routine perinatal care was extracted from the local hospital information systems (ORBIS, ViewPoint). Clinical data concerning antibiotic use in pregnancy and basic maternal data was collected from the patient on a predefined case report form. We specifically asked the women for systemic antibiotic use (oral, intravenous). We did not record local antibiotics like vaginal inserts, ointments, eye drops etc.

### Statistical analyses

Descriptive statistics using percentages for prenatal and perinatal parameters and corresponding antibiotic use were carried out. For categorical variables Pearson's-Chi-square test and for continuous variables Mann-Whitney U test were used for calculating statistical significance. The type I error level was set to 0.05. For cross tables, the "No AB" group (no antibiotics during pregnancy and childbirth) was used as a reference for P values in the "AB total" column, the "No prenatal AB" group (no prenatal antibiotics but possibly antibiotics during childbirth) was used as a reference for P values in the "Prenatal AB" column and the "No AB birth" group (no antibiotics during childbirth but possibly prenatal antibiotics) was used as a reference for P values in the "AB birth" column. All statistical analyses were performed with SPSS 27.0 software (IBM SPSS Statistics for Windows, Version 27.0. Munich, Germany). After univariate analyses, we performed logistic regression models and included the variables and risk factors for antibiotic exposure which were statistically significant in the univariate analysis (▶ **Table 1**): For total antibiotic exposure we included twin pregnancy, previous preterm birth, gestational age at birth, body mass index (BMI), maternal age, gravidity, and hospital admission during pregnancy into the logistic regression model. For prenatal antibiotic exposure we included gestational age at birth, parity, smoking, and hospital admission during pregnancy into the logistic regression model. For antibiotics at birth we included maternal age, twin pregnancy, gestational age at birth, BMI, and hospital admission during pregnancy into the regression model.

## Results

### Cohort characteristics

Between January 2020 and March 2021, we included n = 522 postpartum women into our study (see ▶ **Fig. 1**). N = 258 women were included after personal contact on the maternity ward, n = 157 after contact via mail and n = 109 after phone contact. During the same time, there were n = 2077 births at our hospital. Of those, n = 820 women were contacted and asked to participate in the study. 522 of 820 (66.7%) women signed the written informed consent form and were included into the analysis. The gestational age at birth was 38.3 weeks for the total cohort, 16.5% of the women had a preterm birth. There were 23 twin pregnancies (4.4%). The total cesarean section (CS) rate was 36.3%. The mean BMI at the beginning of pregnancy was 25.3 kg/m$^2$. The incidence of diabetes in pregnancy was 15.1%. N = 185 women from our cohort did not take any systemic antibiotics during pregnancy and childbirth (35.4%). N = 337 women (64.6%) were exposed to antibiotics during pregnancy and/or childbirth. N = 115 women received antibiotics during pregnancy, n = 291 during birth. N = 69 women were treated during pregnancy as well as during childbirth.

Of the 86 women who had a preterm birth, 82 were exposed to antibiotics during pregnancy and childbirth (95.3%). 27 of 86 women received antibiotics during pregnancy and 75 of 86 during childbirth. The mean gestational age at birth for this subcohort was 34.0 weeks (± 2.5 weeks).

### Antibiotic versus no antibiotic use during pregnancy and childbirth

Women who were exposed to antibiotics during pregnancy and/or during childbirth (AB total, see ▶ **Table 1**) had a higher maternal age (p = 0.017) and a higher gravidity (p = 0.045) than women not exposed. There were more twin pregnancies in the AB total group (p = 0.006), the women gave birth at a lower gestational age (p < 0.001) and had more preterm births (p < 0.001). 56.7% of the AB total group gave birth by CS and were consequently exposed to the surgical antimicrobial prophylaxis before skin incision. Women from the exposed group had a higher BMI (p = 0.019), a higher gravidity (p = 0.045) and were more frequently admitted to the hospital during pregnancy (p = 0.001).

### Prenatal antibiotic use

N = 115 women of our cohort used antibiotics during pregnancy. Compared to women who did not use antibiotics during pregnancy, they gave birth at a lower gestational age (p = 0.004), more often had a preterm birth (p = 0.022), were more commonly admitted to the hospital during pregnancy (p = 0.006), had a lower parity (p = 0.024), and more commonly smoked (p = 0.004, see ▶ **Table 1**). Most antibiotics during pregnancy were prescribed for urinary tract infections (56.0%, see ▶ **Fig. 2**), followed by respiratory infections (14.7%) and other infections (7.8%). Most prescriptions were done by obstetrics and gynecology physicians (65.8%), followed by hospitals (16.7%) and family medicine physicians (8.8%, see ▶ **Fig. 3**).

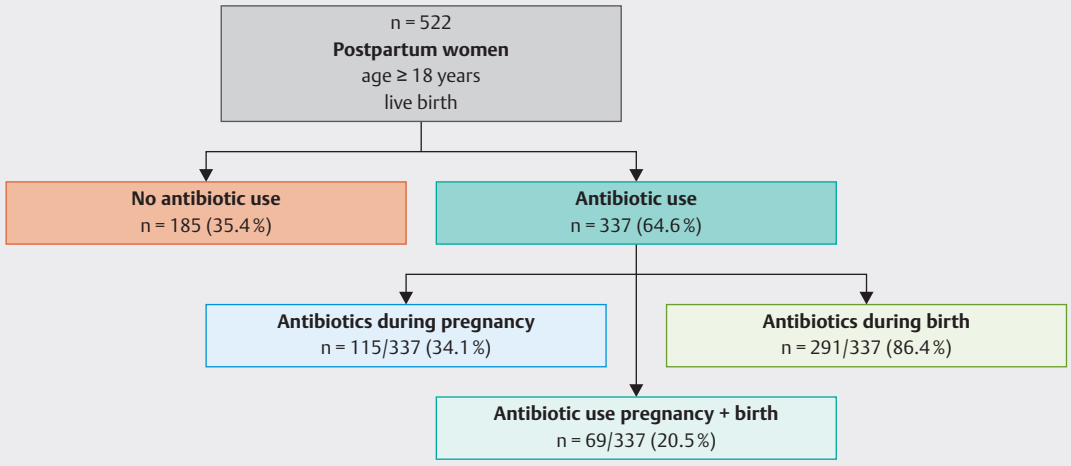
### Antibiotics during childbirth

N = 291 women were exposed to antibiotics during childbirth (AB birth group). Women from the AB birth group had a higher maternal age than women not exposed during birth (p = 0.011), more often had twin pregnancies (p < 0.001), had a lower gestational age at birth (p < 0.001) and more preterm deliveries (p < 0.001, see ▶ **Table 1**). 66% of them gave birth by CS. They also had a higher BMI (p = 0.001) and were more often hospitalized during pregnancy (p = 0.001). The indications for the administration of antibiotics during birth are depicted in ▶ **Fig. 4**. Most women from the AB birth group received the antibiotics for a CS (64.3%), followed by preterm rupture of membranes (PROM, 41.2%), preterm birth (16.2%), Group B streptococci (GBS, 15.1%) and suspected chorioamnionitis (5.8%).

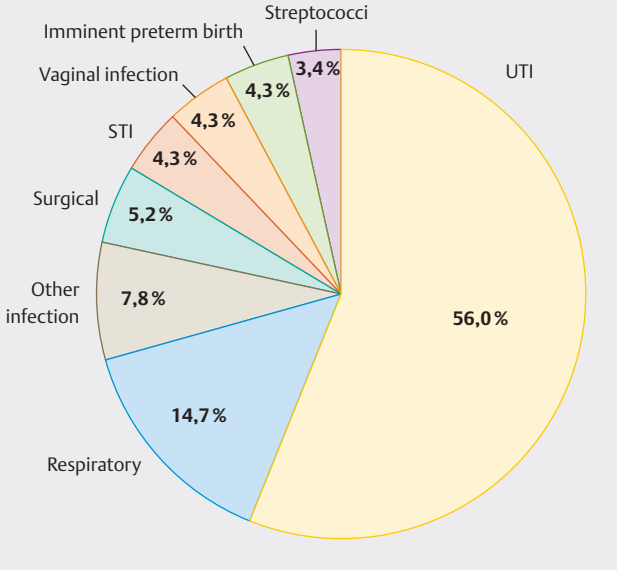
▶**Table 1** Cohort characteristics.

| | **Total Cohort** N = 522 | **No AB** N = 185 | **AB total*** N = 337 | **AB pregnancy#** N = 115 | **AB birth+** n = 291 |
|---|---|---|---|---|---|
| **Origin, n (%)** | | | **p = 0.034** | p = 0.801 | p = 0.158 |
| Germany | 445 (85.2) | 160 (86.5) | 285 (84.6) | 102 (88.7) | 245 (84.2) |
| Europe + Russia | 38 (7.3) | 14 (7.6) | 24 (7.1) | 7 (6.1) | 22 (7.6) |
| Americas | 2 (0.4) | 1 (0.5) | 1 (0.3) | 0 (0) | 1 (0.3) |
| Asia | 16 (3.1) | 9 (4.9) | 7 (2.1) | 2 (1.7) | 6 (2.1) |
| Africa | 8 (1.5) | 0 (0.0) | 8 (2.4) | 1 (0.9) | 7 (2.4) |
| Middle East/Turkey/Northern Africa | 13 (2.5) | 1 (0.5) | 12 (3.6) | 3 (2.6) | 10 (3.4) |
| **Highest Education, n (%)** | | | p = 0.339 | **p = 0.03** | p = 0.946 |
| University | 194 (37.6) | 69 (38.1) | 125 (37.3) | 37 (32.5) | 108 (37.4) |
| Vocational School | 165 (32.0) | 52 (28.7) | 113 (33.7) | 44 (38.6) | 96 (33.2) |
| Secondary school, 12–13 years | 46 (8.9) | 22 (12.2) | 24 (7.2) | 5 (4.4) | 23 (8.0) |
| Secondary school, 10 years | 52 (10.1) | 15 (8.3) | 37 (11.0) | 17 (14.9) | 30 (10.4) |
| Secondary school, 9 years | 25 (4.8) | 9 (5.0) | 16 (4.8) | 7 (6.1) | 14 (4.8) |
| No school degree | 34 (6.6) | 14 (7.7) | 20 (6.0) | 4 (3.5) | 18 (6.2) |
| Maternal age, mean (SD) | 32.0 (4.8) | 31.4 (4.7) | 32.3 (4.9)<br>**p = 0.017** | 31.9 (4.9)<br>p = 0.972 | 32.4 (4.9)<br>**p = 0.011** |
| Gravidity, mean (SD) | 2.2 (1.4) | 2.0 (1.3) | 2.2 (1.4)<br>**p = 0.045** | 2.2 (1.2)<br>p = 0.171 | 2.2 (1.4)<br>p = 0.235 |
| Parity, mean (SD) | 0.7 (0.9) | 0.6 (0.8) | 0.8 (0.9)<br>p = 0.182 | 0.8 (0.9)<br>**p = 0.024** | 0.7 (0.9)<br>p = 0.918 |
| Twin pregnancy, n (%) | 23 (4.4) | 2 (1.1) | 21 (6.2)<br>**p = 0.006** | 6 (5.2)<br>p = 0.631 | 21 (7.2)<br>**p < 0.001** |
| GA at birth, weeks, mean (SD) | 38.3 (2.4) | 39.3 (1.2) | 37.7 (2.7)<br>**p < 0.001** | 37.6 (3.0)<br>**p = 0.004** | 37.6 (2.7)<br>**p < 0.001** |
| Preterm birth, n (%) | 86 (16.5) | 4 (2.2) | 82 (24.3)<br>**p < 0.001** | 27 (23.5)<br>**p = 0.022** | 75 (25.8)<br>**p < 0.001** |
| **Mode of birth, n (%)** | | | **p < 0.001** | p = 0.858 | **p < 0.001** |
| Cesarean section | 186 (36.3) | 0 (0.0) | 186 (56.7) | 43 (37.7) | 186 (66.0) |
| Vaginal birth | 310 (60.4) | 179 (96.8) | 181 (39.9) | 68 (59.6) | 88 (31.2) |
| Operative vaginal birth | 17 (3.3) | 6 (3.2) | 11 (3.4) | 3 (2.6) | 8 (2.8) |
| Previous preterm birth, n (%) | 51 (9.8) | 10 (5.4) | 41 (12.2)<br>**p = 0.013** | 16 (13.9)<br>p = 0.09 | 33 (11.3)<br>p = 0.175 |
| Diabetes, n (%) | 79 (15.1) | 24 (13.0) | 55 (16.3)<br>p = 0.307 | 19 (16.5)<br>p = 0.638 | 45 (15.5)<br>p = 0.813 |
| BMI, mean (SD) | 25.3 (6.8) | 24.2 (4.6) | 25.9 (6.8)<br>**p = 0.019** | 25.2 (5.4)<br>p = 0.702 | 26.3 (7.1)<br>**p = 0.001** |
| Smoking, n (%) | 24 (4.6) | 8 (4.3) | 16 (4.7)<br>p = 0.825 | 11 (9.6)<br>**p = 0.004** | 13 (4.5)<br>p = 0.873 |
| Inpatient in pregnancy, n (%) | 95 (18.2) | 19 (10.3) | 76 (22.6)<br>**p = 0.001** | 31 (27.0)<br>**p = 0.006** | 68 (23.4)<br>**p = 0.001** |

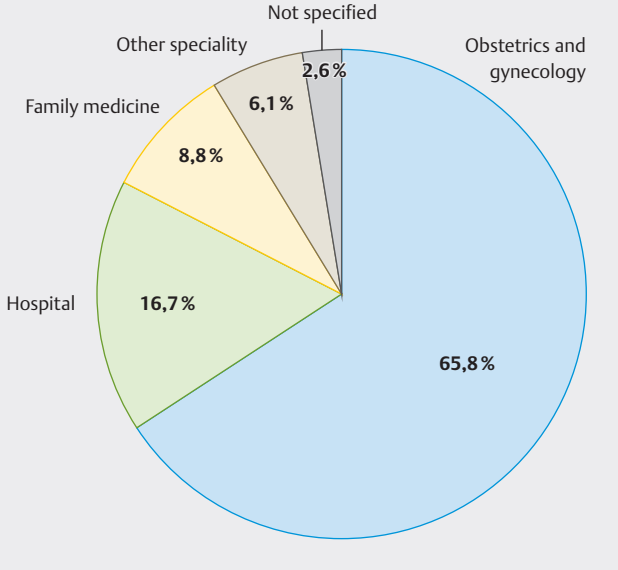
P values were derived from Pearson's Chi-square Test for categorial variables and Mann-Whitney-U-Test for continuous variables. Percentages are given as column percentages. * The "No AB" group was used as a reference for P values in the "AB total" column. # The "No AB pregnancy" group was used as a reference for P values in the "AB pregnancy" column. +The "No AB birth" group was used as a reference for P values in the "AB birth" column (see methods section).




▶ **Fig. 1** Study Flowchart.




▶ **Fig. 2** Indications for antibiotic therapy in pregnancy (excluding childbirth). N = 115 women from this cohort used antibiotics during pregnancy. They were asked for the indication for the antibiotic prescription. If a patient got antibiotics more than once during pregnancy, the indication for the first course was used.



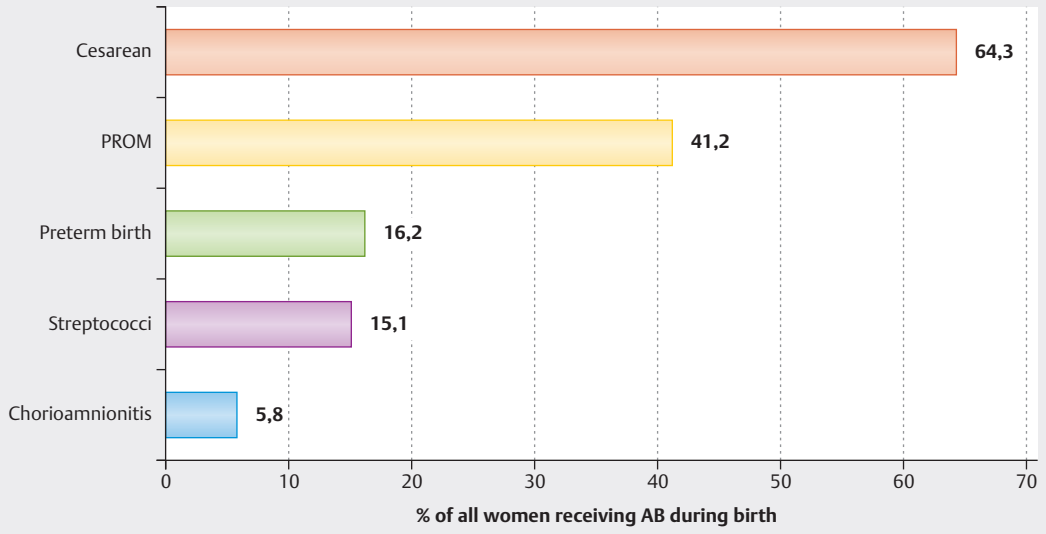

▶ **Fig. 3** Specialties of physicians prescribing antibiotics to pregnant women during pregnancy. N = 115 women from this cohort took antibiotics during pregnancy. They were asked who prescribed the antibiotics to them. If a patient got antibiotics more than once during pregnancy, the prescriber for the first course was used.

### Risk factors for antibiotic treatment

We further evaluated the variables/risk factors which showed a significant association with antibiotic use in the univariate analysis (▶ **Table 1**) in three different logistic regression models. For total AB use, maternal BMI (OR 1.07, 95% CI 1.03–1.11, p = 0.001) and gestational age at birth (OR 0.67, 95% CI 0.58–0.76, p < 0.001) showed an independent association with antibiotic exposure. For prenatal antibiotic use, gestational age at birth (OR 0.89, 95% CI 0.82–0.97, p = 0.006) and smoking (OR 3.21, 95% CI 1.38–7.46, p = 0.007) were independently associated with antibiotic treatment. For antibiotics at birth, maternal BMI (OR 1.09, 95% CI 1.05–1.13, p < 0.001) and gestational age at birth (OR 0.71, 95% CI 0.64–0.80, p < 0.001) were independent risk factors for an antibiotic treatment.

## Discussion

We present data from a single center prospective observational study on the prevalence, indications, and prescribing patterns of antibiotic treatment during pregnancy and childbirth. Almost 65 %




▶ **Fig. 4** Indications for antibiotic use during childbirth. N = 291 women received antibiotics during childbirth. The figure depicts the indications for its administration. There could be more than one indication.

of mother-infant pairs of our cohort were exposed to antibiotics, most of them during birth (86.4%). Thus, most neonates have had contact to antibiotics even before they were born. Over 95% of women who had a preterm birth were exposed to antibiotics during pregnancy and birth.

There is no doubt about the importance of anti-infective drugs in perinatal medicine. Maternal sepsis was the cause of 9.7% of maternal deaths globally, being responsible for a total of 23717 deaths in 2013 [2]. Maternal infectious morbidity and mortality has a direct effect on newborn health [1]. Hence, the availability of effective antibiotics is a major public health issue in perinatal medicine. On the contrary, an overuse of antibiotics leads to unnecessary side effects and a rise of resistant bacteria. But how much is too much? This question is asked by more and more experts in the field of perinatal infectious diseases [24]. Almost 65% of our cohort was exposed to antibiotics during pregnancy and childbirth. Current data on the use of antibiotics in pregnancy is sparse. A register-based cohort study from Denmark published in 2014 reports on outpatient antibiotic prescriptions in pregnancy over a ten-year period. They found that 33.4% of all pregnant women had used systemic antibiotics in the year 2000 which increased to 37% in 2010 [25]. As this study did not include hospital medications, their data is only comparable to our subgroup "AB in pregnancy" (n = 115 of 522 pregnancies, 22.0%). The authors describe obesity, young maternal age, and lower education as risk factors for prenatal antibiotic use. A population-based cohort study from Italy found a rate of 27% for prenatal antibiotic exposure from 2007 to 2017, also not including hospital medications [26]. They focused on neonatal outcomes and report an increased risk of preterm birth, low birth weight and low APGAR scores with antibiotic use in pregnancy. There seems to be a wide variation of outpatient antibiotic prescriptions between countries and continents. A trial on antibiotics in ambulatory care in China only found a prescription rate of only 2% [27]. Observational data from Germany described outpatient prescriptions of antibiotics to 15% of pregnant women from 2005 to 2014 [28]. Older data from 2006 found a rate of 20% in the outpatient setting, 1.3% received substances which are contraindicated in pregnancy [29]. There is no German data on the use of antibiotics during hospital stays and especially birth except for a doctoral thesis from Jena which showed an antibiotic exposition of 24% of vaginal births at term in the years 2013/14 [30]. The national perinatal statistic by the Institute for Quality Assurance and Transparency in Healthcare (IQTIG) only mentions the surgical antimicrobial prophylaxis for caesarean section, which 99% of pregnant women received in 2020 [31].

In our study, most antibiotics in pregnancy were prescribed for urinary tract infections (UTIs). Symptomatic UTIs are common and effect 1–2% of all pregnancies. As they increase the risk for pyelonephritis, they should be treated with antibiotics [14]. Importantly, guidelines recommend a urine culture before the start of treatment for all pregnant women [14, 32]. The evidence for asymptomatic bacteriuria in pregnancy is less clear. It is defined as a significant level of bacteria in the urine without any symptoms and affects 5 to 10% of pregnancies [33]. It increases the risk for symptomatic UTI and pyelonephritis. German guidelines do not recommend screening for and treatment of asymptomatic bacteriuria anymore [14, 34], based on data from a Dutch randomized controlled trial (RCT), which did not show a significant association of asymptomatic bacteriuria with preterm birth [35], but there is no international consensus. As 12.5% of our cohort received antibiotics for UTI which is a lot more than reported in literature, it can be suspected that there is potential for antibiotic stewardship in this indication.

During childbirth, 55.7% of our cohort received antibiotics. The indications included CS, PROM, preterm birth, GBS prevention and suspected chorioamnionitis. 36.3% of women in our cohort gave birth by CS. The CS rate in Germany was 32.2% in 2020 [31]. All surgical procedures can be complicated by surgical site infections.

For example, wound infections affect 2 to 7% of women with CS and endometritis affects 2 to 16% [36]. Thus, prophylactic antibiotics are international standard for CS and significantly reduce maternal infectious complications [12]. Until 2013, prophylactic antibiotics for CS were given after cord clamping [37]. As large trials and meta-analyses revealed a lower risk for complications when antibiotics are given before skin incision [11, 38, 39], guidelines changed and now recommend the administration of antibiotics 30 to 120 minutes before skin incision [40, 41, 42]. This, however, leads to an intrauterine exposure to antibiotics of all infants born by CS and there is evidence that even a single dose of antibiotics has an impact on early neonatal gut microbiome development [43]. A recent prospective multicenter study from Switzerland did not find an increased risk for infections in mothers who received the antibiotic after cord clamping. It was the largest clinical study on the topic so far [44]. However, infectious morbidity after birth can be a severe maternal health risk, disturbs maternal care for the newborn and potentially leads to postpartum antibiotic treatment which transfers to the infant via breast milk. Prospective RCTs are needed to evaluate if a surgical antimicrobial prophylaxis for CS is needed in every obstetric setting, especially in low-risk situations like elective CS with intact membranes in facilities with good hygiene standards and adequate postpartum care. By this, a safe reduction of perinatal antibiotic exposure could be achieved.

A large proportion of our cohort received intrapartum antibiotics because of PROM, preterm birth or GBS carrier status. In total, 96 of 327 women (29.4%) with vaginal birth received antibiotics. Intrapartum antibiotic prophylaxis is most commonly given to prevent neonatal GBS disease including sepsis, meningitis, and pneumonia by vertical transmission. There are two strategies to prevent early-onset GBS infection: risk-based versus screening-based protocols [45]. In Germany, a mixture of both is practiced. While a 2016 national guideline by neonatal and obstetric societies recommends a universal GBS screening between 35 and 37 weeks [46], the German maternity guidelines do not include the culture-based approach during prenatal care and it is not covered by many health insurances [47]. Therefore, women with unknown GBS status are common and are treated with intrapartum antibiotics based on the risk-based strategy. Intrapartum antibiotics are administered to

1. GBS positive women and
2. women with unknown GBS status who meet one of the following criteria: preterm birth, PROM for more than 12 hours or temperature >/= 38.0 °C [34, 46].

There is no international consensus on the optimal approach to GBS prevention. In terms of antibiotic exposure, risk- and screening-based strategies both lead to antibiotic treatment of many healthy women and fetuses. Even if universal GBS screening by a single culture at 35 to 37 weeks of GA was implemented, over 99% of mother infant pairs with positive screening would be exposed to antibiotics without a personal benefit [48]. Therefore, further research is needed to better identify women and infants at risk for GBS disease. An intrapartum PCR assay for GBS and a GBS vaccination are discussed as efforts to reduce the global burden of GBS disease [49, 50]. They would also help to reduce intrapartum antibiotic exposure affecting 29.4% of women with vaginal birth in this cohort, which is in line with published data [45].

Over 95% of preterm neonates were exposed to antibiotics prenatally in our study. Preterm birth increases the risk for neonatal infections and special caution needs to be taken including perinatal antibiotic treatment [51]. Preterm infants are more often born by cesarean section or receive intrapartum antibiotics to prevent early onset sepsis. Furthermore, they are often treated with antibiotics during early life. Taken together, almost all preterm infants are exposed to perinatal antibiotics which influences neonatal gut microbiome development and has potential long term health consequences [16, 52].

We are aware of strengths and limitations of our study. A major strength is the prospective design and the structured data acquisition with a predefined data set. The design made it possible to collect reliable information by the women themselves on antibiotic use during pregnancy and childbirth. Most published trials on this topic use prescription data from registries, which is usually limited to ambulatory settings. We are also aware of some limitations. One limitation is the relatively small cohort size (n = 522), a second one is the single center design of our study. As standards of care and patient characteristics differ between regions and hospitals, our results may not be fully transferable to other populations.

## Conclusions

A majority of mothers and infants are prenatally exposed to antibiotics during pregnancy and childbirth. As overuse of antibiotics increases antimicrobial resistance, has an impact on neonatal gut microbiome development as well as potential long term health consequences, there is a need for antibiotic stewardship programs and antimicrobial surveillance in perinatal medicine. Furthermore, more research is needed to limit the use of perinatal antibiotics to high-risk populations and achieve a safe reduction of antibiotic exposure of mothers and infants during pregnancy and birth.

## Compliance with Ethical Standards

**Funding:** This study did not receive any funding.

**Ethical approval:** Approval by the local ethics committee for research in human subjects of the University of Lübeck has been granted (Reference number 20-063).

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### Conflict of Interest

The authors declare that they have no conflict of interest.

## References


[1] Gülmezoglu AM, Lawrie TA, Hezelgrave N, Oladapo OT, Souza JP, Gielen M, Lawn JE, Bahl R, Althabe F, Colaci D, Hofmeyr GJ. Interventions to Reduce Maternal and Newborn Morbidity and Mortality. Black RE, Laxminarayan R, Temmerman M, Walker N (eds.). Reproductive, Maternal, Newborn, and Child Health. Disease Control Priorities, Third Edition (Volume 2). Washington (DC): The International Bank for Reconstruction and Development/The World Bank; 2016: 115–136

[2] Kassebaum NJ, Bertozzi-Villa A, Coggeshall MS et al. Global, regional, and national levels and causes of maternal mortality during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014; 384: 980–1004. doi:10.1016/S0140-6736(14)60696-6

[3] Johnson CT, Adami RR, Farzin A. Antibiotic therapy for chorioamnionitis to reduce the global burden of associated disease. Front Pharmacol 2017; 8: 97. doi:10.3389/fphar.2017.00097

[4] Thinkhamrop J, Hofmeyr GJ, Adetoro O et al. Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity. Cochrane Database Syst Rev 2015(6): CD002250. doi:10.1002/14651858.CD002250.PUB3

[5] Kenyon S, Boulvain M, Neilson JP. Antibiotics for preterm rupture of membranes. Cochrane Database Syst Rev 2013(12): CD001058. doi:10.1002/14651858.CD001058.pub3

[6] European Centre for Disease Prevention and Control. Antimicrobial consumption in the EU/EEA (ESAC-Net) – Annual Epidemiological Report for 2020. Accessed July 20, 2022 at: https://www.ecdc.europa.eu/sites/default/files/documents/ESAC-Net%20AER-2020-Antimicrobial-consumption-in-the-EU-EEA.pdf

[7] Robertson J, Vlahović-Palčevski V, Iwamoto K et al. Variations in the Consumption of Antimicrobial Medicines in the European Region, 2014–2018: Findings and Implications from ESAC-Net and WHO Europe. Front Pharmacol 2021; 12: 639207. doi:10.3389/fphar.2021.639207

[8] Dyar OJ, Huttner B, Schouten J et al. What is antimicrobial stewardship? Clin Microbiol Infect 2017; 23: 793–798. doi:10.1016/J.CMI.2017.08.026

[9] World Health Organization. Antimicrobial resistance: global report on surveillance. World Health Organization. 2014. Accessed July 20, 2022 at: https://apps.who.int/iris/handle/10665/112642

[10] Schweickert B, Feig M, Schneider M et al. Antibiotic consumption in Germany: first data of a newly implemented web-based tool for local and national surveillance. J Antimicrob Chemother 2018; 73: 3505–3515. doi:10.1093/JAC/DKY345

[11] Mackeen AD, Packard RE, Ota E et al. Timing of intravenous prophylactic antibiotics for preventing postpartum infectious morbidity in women undergoing cesarean delivery. Cochrane Database Syst Rev 2014(12): CD00951. doi:10.1002/14651858.CD009516.pub2

[12] Smaill FM, Grivell RM. Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. Cochrane Database Syst Rev 2014(10): CD00748. doi:10.1002/14651858.CD007482.pub3

[13] Schrag S, Gorwitz R, Fultz-Butts K et al. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC. MMWR Recomm Rep 2002; 51: 1–22

[14] DGU. Interdisziplinäre S3 Leitlinie: Epidemiologie, Diagnostik, Therapie, Prävention und Management unkomplizierter, bakterieller, ambulant erworbener Harnwegsinfektionen bei erwachsenen Patienten. AWMF-Registernummer: 043/044. 2017. Accessed July 20, 2022 at: https://www.awmf.org/uploads/tx_szleitlinien/043–044l_S3_Harnwegsinfektionen_2017–05.pdf

[15] Mazzola G, Murphy K, Ross RP et al. Early gut microbiota perturbations following intrapartum antibiotic prophylaxis to prevent group B streptococcal disease. PLoS One 2016; 11: e0157527. doi:10.1371/journal.pone.0157527

[16] Tapiainen T, Koivusaari P, Brinkac L et al. Impact of intrapartum and postnatal antibiotics on the gut microbiome and emergence of antimicrobial resistance in infants. Sci Rep 2019; 9: 10635. doi:10.1038/s41598-019-46964-5

[17] Rautava S. Early microbial contact, the breast milk microbiome and child health. J Dev Orig Health Dis 2016; 7: 5–14. doi:10.1017/S2040174415001233

[18] Gosalbes MJ, Vallès Y, Jiménez-Hernández N et al. High frequencies of antibiotic resistance genes in infants' meconium and early fecal samples. J Dev Orig Health Dis 2016; 7: 35–44. doi:10.1017/S2040174415001506

[19] Nogacka A, Salazar N, Suárez M et al. Impact of intrapartum antimicrobial prophylaxis upon the intestinal microbiota and the prevalence of antibiotic resistance genes in vaginally delivered full-term neonates. Microbiome 2017; 5: 93. doi:10.1186/s40168-017-0313-3

[20] Zhang M, Differding MK, Benjamin-Neelon SE et al. Association of prenatal antibiotics with measures of infant adiposity and the gut microbiome. Ann Clin Microbiol Antimicrob 2019; 18: 18. doi:10.1186/s12941-019-0318-9

[21] Lapin B, Piorkowski J, Ownby D et al. Relationship between prenatal antibiotic use and asthma in at-risk children. Ann Allergy Asthma Immunol 2015; 114: 203–207. doi:10.1016/j.anai.2014.11.014

[22] Baron R, Taye M, der Vaart IB et al. The relationship of prenatal antibiotic exposure and infant antibiotic administration with childhood allergies: A systematic review. BMC Pediatr 2020; 20. doi:10.1186/s12887-020-02042-8

[23] Rasmussen SH, Shrestha S, Bjerregaard LG et al. Antibiotic exposure in early life and childhood overweight and obesity: A systematic review and meta-analysis. Diabetes Obes Metab 2018; 20: 1508–1514. doi:10.1111/dom.13230

[24] Mendling W. Geschichte und Gegenwart der infektiologie in der Frauenheilkunde und Geburtshilfe Deutschlands: Eine Bestandsaufnahme anlässlich des 30-jährigen Bestehens der Arbeitsgemeinschaft für Infektionen und Infektionsimmunologie in der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe (AGII). Geburtshilfe Frauenheilkd 2018; 78: 130–142. doi:10.1055/s-0043-122194

[25] Broe A, Pottegård A, Lamont RF et al. Increasing use of antibiotics in pregnancy during the period 2000–2010: prevalence, timing, category, and demographics. BJOG 2014; 121: 988–996. doi:10.1111/1471-0528.12806

[26] Cantarutti A, Rea F, Franchi M et al. Use of antibiotic treatment in pregnancy and the risk of several neonatal outcomes: A population-based study. Int J Environ Res Public Health 2021; 18: 12621. doi:10.3390/ijerph182312621

[27] Zhao H, Zhang M, Bian J et al. Antibiotic prescriptions among china ambulatory care visits of pregnant women: A nationwide cross-sectional study. Antibiotics (Basel) 2021; 10: 601. doi:10.3390/antibiotics10050601

[28] Jacob L, Kalder M, Kostev K. Prevalence and predictors of prescription of antibiotics in pregnant women treated by gynecologists in Germany. Int J Clin Pharmacol Ther 2017; 55: 643–649. doi:10.5414/CP202946

[29] Amann U, Egen-Lappe V, Strunz-Lehner C et al. Antibiotics in pregnancy: Analysis of potential risks and determinants in a large German statutory sickness fund population. Pharmacoepidemiol Drug Saf 2006; 15: 327–337. doi:10.1002/PDS.1225

[30] Stoychovska DE. Prä- und postnatale Antibiotikaexposition: eine Beobachtungsstudie mit Daten aus drei Frauenkliniken in den Jahrgängen 2013/2014 [Dissertation]. Jena: Friedrich-Schiller-Universität; 2017.

[31] IQTIG. Bundesauswertung zum Erfassungsjahr 2020 Geburtshilfe. Berlin: IQTIG – Institut für Qualitätssicherung und Transparenz im Gesundheitswesen;2021. Accessed July 20, 2022 at: https://iqtig.org/downloads/auswertung/2020/16n1gebh/QSKH_16n1-GEBH_2020_BUAW_V01_2021-08-10.pdf

[32] NICE. Urinary tract infection (lower): antimicrobial prescribing. NICE guideline 109. 2018. Accessed October 26, 2022 at: https://www.nice.org.uk/guidance/ng109/resources/urinary-tract-infection-lower-antimicrobial-prescribing-pdf-66141546350533

[33] Guinto VT, De Guia B, Festin MR et al. Different antibiotic regimens for treating asymptomatic bacteriuria in pregnancy. Cochrane Database Syst Rev 2010(9): CD007855. doi:10.1002/14651858.cd007855.pub2

[34] Berger R, Abele H, Bahlmann F et al. Prevention and Therapy of Preterm Birth. Guideline of the DGGG, OEGGG and SGGG (S2k Level, AWMF Registry Number 015/025, February 2019) - Part 1 with Recommendations on the Epidemiology, Etiology, Prediction, Primary and Secondary Prevention of Preterm Birth. Geburtshilfe Frauenheilkd 2019; 79: 800–812. doi:10.1055/A-0903-2671

[35] Kazemier BM, Koningstein FN, Schneeberger C et al. Maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy: a prospective cohort study with an embedded randomised controlled trial. Lancet Infect Dis 2015; 15: 1324–1333. doi:10.1016/S1473-3099(15)00070-5

[36] Kawakita T, Landy HJ. Surgical site infections after cesarean delivery: epidemiology, prevention and treatment. Matern Heal Neonatol Perinatol 2017; 3: 12. doi:10.1186/s40748-017-0051-3

[37] Hopkins L, Smaill FM. WITHDRAWN: Antibiotic prophylaxis regimens and drugs for cesarean section. Cochrane Database Syst Rev 2012(1): CD001136. doi:10.1002/14651858.cd001136.pub2

[38] Kalaranjini S, Veena P, Rani R. Comparison of administration of single dose ceftriaxone for elective caesarean section before skin incision and after cord clamping in preventing post-operative infectious morbidity. Arch Gynecol Obstet 2013; 288: 1263–1268. doi:10.1007/s00404-013-2906-9

[39] Kandil M, Sanad Z, Gaber W. Antibiotic prophylaxis at elective cesarean section: A randomized controlled trial in a low resource setting. J Matern Neonatal Med 2014; 27: 588–591. doi:10.3109/14767058.2013.823938

[40] The American College of Obstetricians and Gynecologists. Committee opinion no. 465: Antimicrobial prophylaxis for cesarean delivery: Timing of administration. Obstet Gynecol 2010; 116: 791–792. doi:10.1097/AOG.0b013e3181f68086

[41] Macones GA, Caughey AB, Wood SL et al. Guidelines for postoperative care in cesarean delivery: Enhanced Recovery After Surgery (ERAS) Society recommendations (part 3). Am J Obstet Gynecol 2019; 221: 247.e1–247.e9. doi:10.1016/J.AJOG.2019.04.012

[42] Louwen F, Wagner U, Abou-Dakn M et al. Caesarean section. Guideline of the DGGG, OEGGG and SGGG (S3-level, AWMF Registry No. 015/084, June 2020). Geburtshilfe Frauenheilkd 2021; 81: 896–921. doi:10.1055/A-1529-6141

[43] Bossung V, Lupatsii M, Dashdorj L et al. Timing of antimicrobial prophylaxis for cesarean section is critical for gut microbiome development in term born infants. Gut Microbes 2022; 14: 2038855. doi:10.1080/19490976.2022.2038855

[44] Sommerstein R, Marschall J, Atkinson A et al. Antimicrobial prophylaxis administration after umbilical cord clamping in cesarean section and the risk of surgical site infection: a cohort study with 55,901 patients. Antimicrob Resist Infect Control 2020; 9: 201. doi:10.1186/s13756-020-00860-0

[45] Hasperhoven GF, Al-Nasiry S, Bekker V et al. Universal screening versus risk-based protocols for antibiotic prophylaxis during childbirth to prevent early-onset group B streptococcal disease: a systematic review and meta-analysis. BJOG 2020; 127: 680–691. doi:10.1111/1471-0528.16085

[46] GNPI. Prophylaxe der Neugeborenensepsis – frühe Form – durch Streptokokken der Gruppe B. S2k, AWMF Registernummer 024/020. 2016. Accessed October 26, 2022 at: https://gnpi.de/wp-content/uploads/2020/07/024-020l_S2k_Prophylaxe_Neugeborenensepsis_Streptokokken_2016-04.pdf

[47] Gemeinsamer Bundesausschuss. Richtlinien des Gemeinsamen Bundesausschusses über die ärztliche Betreuung während der Schwangerschaft und nach der Entbindung („Mutterschafts-Richtlinien“). Bundesanzeiger Nr 60 a vom 27 März 1986; zuletzt geändert am 16 Sept 2021 veröffentlicht im Bundesanzeiger 26 112 021 B4 Kraft getreten am 1 Jan 2022 2021 1985

[48] Seedat F, Geppert J, Stinton C et al. Universal antenatal screening for group B streptococcus may cause more harm than good. BMJ 2019; 364: l463. doi:10.1136/BMJ.L463

[49] Lawn JE, Chandna J, Paul P et al. Every Country, Every Family: Time to Act for Group B Streptococcal Disease Worldwide. Clin Infect Dis 2022; 74: S1–S4. doi:10.1093/CID/CIAB859

[50] Khalil MR, Uldbjerg N, Thorsen PB et al. Intrapartum PCR assay versus antepartum culture for assessment of vaginal carriage of group B streptococci in a Danish cohort at birth. PLoS One 2017; 12: e0180262. doi:10.1371/journal.pone.0180262

[51] Lin FYC, Weisman LE, Troendle J et al. Prematurity is the major risk factor for late-onset group B streptococcus disease. J Infect Dis 2003; 188: 267–271. doi:10.1086/376457

[52] Dierikx TH, Visser DH, Benninga MA et al. The influence of prenatal and intrapartum antibiotics on intestinal microbiota colonisation in infants: A systematic review. J Infect 2020; 81: 190–204. doi:10.1016/j.jinf.2020.05.002