Thieme

Antibiotic Treatment During Pregnancy and the First Six Months Postpartum – a Secondary Analysis of the "Healthy Living in Pregnancy" (GeliS) Study

Antibiotikabehandlung während der Schwangerschaft und den ersten 6 postpartalen Monaten – eine Sekundäranalyse der Studie „Gesund leben in der Schwangerschaft" (GeliS)

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ABSTRACT

Introduction

Antibiotic therapies for the treatment of bacterial infections pose a particular challenge during pregnancy and breastfeeding. For Germany, there is hardly any information on the frequency of antibiotic use during this phase. Our analysis uses data from the "Healthy Living in Pregnancy" (GeliS) study to describe antibiotic treatments during pregnancy and in the first six months after birth (postpartum), and to compare their use with existing recommendations.

Methods

This is a retrospective secondary analysis of the GeliS study. In the cluster randomized lifestyle intervention study, detailed information on antibiotic therapies during pregnancy and postpartum was collected using surveys. Chi-square tests and generalized estimating equations were used for evaluation.

Results

Of the 1636 women included in the analysis, 21% reported antibiotic treatment at least once during pregnancy (14%) or in the first six months postpartum (7%). During pregnancy, the antibiotic therapies of women increased from 1.7% in the first trimester to 6.5% in the third trimester. Common reasons for treatment were urinary tract infections (7.3% of women), ear, nose, throat (ENT) infections (3.6%), and birth complications (2.6%). The information on the prescribed preparations corresponded to the current recommendations. A significant increase in the frequency of treatment with antibiotics was observed in the lifestyle intervention group ($p < 0.001$), in participants without a partner ($p < 0.001$), and in women who breastfed their children ($p = 0.005$) or gave birth by caesarean section ($p = 0.003$) or

prematurely (p = 0.012). Other socioeconomic or lifestyle factors were not significant.

Conclusion
Approximately one in five women receives at least one antibiotic treatment during pregnancy and breastfeeding that meets current treatment recommendations. Treatment with antibiotics is more common in premature births, caesarean sections, and breastfeeding women.

ABSTRACT

Einleitung
Antibiotikatherapien zur Behandlung bakterieller Infektionen stellen in der Schwangerschaft und Stillzeit eine besondere Herausforderung dar. Für Deutschland gibt es kaum Informationen zur Häufigkeit des Antibiotikaeinsatzes in dieser Phase. Unsere Analyse nutzt Daten der „Gesund leben in der Schwangerschaft“-(GeliS)Studie, um Antibiotikabehandlungen in der Schwangerschaft und in den ersten 6 Monaten nach der Geburt (postpartal) zu beschreiben und deren Einsatz mit den bestehenden Empfehlungen zu vergleichen.

Methoden
Es handelt sich um eine retrospektive Sekundäranalyse der GeliS-Studie. In der clusterrandomisierten Lebensstilinterventionsstudie wurden detaillierte Informationen zu Antibiotikatherapien während der Schwangerschaft und postpartal mittels Fragebogen erhoben. Für die Auswertung wurden Chi-Quadrat-Tests sowie generalisierte Schätzungsgleichungen verwendet.

Ergebnisse
Von 1636 in die Analyse eingeschlossenen Frauen gaben 21 % an, mindestens einmal während der Schwangerschaft (14 %) oder in den ersten 6 Monaten postpartal (7 %) mit Antibiotika behandelt worden zu sein. Im Verlauf der Schwangerschaft nahmen die Antibiotikatherapien der Frauen von 1,7 % im 1. auf 6,5 % im 3. Trimenon zu. Häufige Behandlungsgründe waren Harnwegsinfektionen (7,3 % der Frauen), Hals-Nasen-Ohren-(HNO-)Infekte (3,6 %) und Geburtskomplikationen (2,6 %). Die Angaben zu den verordneten Präparaten entsprachen den aktuellen Empfehlungen. Eine signifikant erhöhte Behandlungshäufigkeit mit Antibiotika zeigte sich in der Lebensstilinterventionsgruppe (p < 0,001), bei Teilnehmerinnen ohne Partner (p < 0,001), sowie bei Frauen, die ihre Kinder gestillt (p = 0,005) oder durch Kaiserschnitt (p = 0,003) oder Frühgeburt (p = 0,012) zur Welt gebracht hatten. Andere sozioökonomische oder den Lebensstil betreffende Faktoren waren nicht signifikant.

Schlussfolgerung
Etwa jede 5. Frau erhält während der Schwangerschaft und Stillzeit mindestens eine Antibiotikabehandlung, die den aktuellen Behandlungsempfehlungen entspricht. Bei Frühgeburten, Kaiserschnittentbindungen und stillenden Frauen wird häufiger mit Antibiotika behandelt.

Introduction

Antibiotics are essential for treating bacterial infections and are among the most commonly prescribed drugs worldwide [1]. Rational use of these preparations must be ensured in order to avoid the development of resistance [2, 3]. For this purpose, guidelines and the concept of “antibiotic stewardship” are available [4]. Some particular features should be considered when treating pregnant women and breastfeeding mothers with antibiotics [5]. For example, certain preparations are associated with an increased risk of malformations in children [5, 6]. In the literature, changes in the fetal microbiome due to antibiotics and the resulting development of obesity or childhood atopic diseases are also discussed [7, 8].

Antibiotic therapies during pregnancy and breastfeeding therefore pose a particular challenge, as the benefits and risks must be weighed appropriately [5, 9, 10, 11, 12, 13]. Since randomized controlled trials in pregnant women are hardly justifiable, the evidence of current treatment guidelines is usually low [5, 14]. However, there are some recommendations [5, 15] and guidelines [16, 17, 18, 19] for antibiotic treatment in pregnancy and breastfeeding. For Germany, there are hardly any analyses to date on the use of antibiotics in this critical phase and on the factors influencing their prescription. It is well known that a high level of education [3, 20], a high level of health awareness, and a stable socioeconomic environment [3, 20, 21] can lead to reduced antibiotic use. However, study results on this issue are inconsistent [21, 22].

The aim of this analysis was to describe potential patterns and determinants of antibiotic treatments during pregnancy and in the first six months after birth using data from the “Healthy Living in Pregnancy” (GeliS) study [23]. The reasons for treatment, the preparations used, and possible influencing factors were also investigated. Another goal was to compare these results with the existing recommendations.

Methods

Design and setting of the GeliS study

This is a retrospective secondary analysis of the GeliS study. It was designed as a cluster randomized intervention study to investigate whether lifestyle intervention during pregnancy can prevent excessive weight gain [23]. The National Academy of Medicine criteria were used to classify excessive weight gain [24]. The participants in the GeliS study were recruited from 71 medical practices in Bavaria as part of routine care [25]. The study protocol was ap-

proved by the Ethics Committee (project number 5653/13) of the Medical Faculty of the Technical University of Munich. The GeliS study was registered in the ClinicalTrials.gov Protocol Registration System (NCT01958307).

Study participants

Between 2013 and 2015, 2286 pregnant women were recruited for the GeliS study. The participants were enrolled in the study before 12 weeks of pregnancy, were between 18 and 43 years of age, and had a body mass index (BMI) ranging from 18.5 to 40.0 kg/m^2. Other selection criteria included sufficient knowledge of the German language and a written declaration of consent. Women with multiple pregnancies, high-risk pregnancies, such as placenta previa, persistent bleeding, cervical insufficiency, and pregnancy-induced high blood pressure or other serious diseases were excluded [23].

The lifestyle intervention in the GeliS study

The women in the intervention group (IG) received structured lifestyle consultations from previously trained practice staff, such as medical assistants, midwives, and gynecologists, at four different points in time (12 th – 16 th week of pregnancy, 16 th – 20 th week of pregnancy, 30 th – 34 th week of pregnancy, 6 – 8 weeks postpartum), which were included in routine care during pregnancy [23]. The consultations were based on the recommendation guidelines of the network "Gesund ins Leben – Netzwerk Junge Familie" [26] and covered topics such as healthy nutrition, supplementation, physical activity, and appropriate weight development during pregnancy and breastfeeding. Participants were also informed about food-related infections, such as toxoplasmosis or listeriosis. At the time of inclusion in the study, the study participants in the control group (CG) were only given a flyer with general information on a healthy lifestyle during pregnancy [23].

Data collection

Information on the participants' anthropometric, demographic, and socioeconomic characteristics was obtained using a screening survey, which was completed before the 12 th week of pregnancy. Data on treatment with antibiotics during pregnancy and in the first six months postpartum were collected retrospectively on average one year after delivery as part of the ex ante planned follow-up of the study. For this purpose, a standardized survey was sent to the mothers around the children's first birthday. In free text fields, the reasons for treatment with antibiotics and information on the drugs (product name and manufacturer information) were queried, with information on the period of use collected separately (see below). The free text responses to antibiotic treatments were systematically evaluated for further data processing and summarized into appropriate groups. The preparations used were assigned to the respective antibiotic class.

The question about the intake period was answered using the following response options:

1. "In the first trimester"
2. "In the second trimester"
3. "In the third trimester"
4. "In the first six months after birth"

The frequency of antibiotic treatment was determined using the following options:

1. "Once"
2. "Twice"
3. "Three times"
4. "≥ four times".

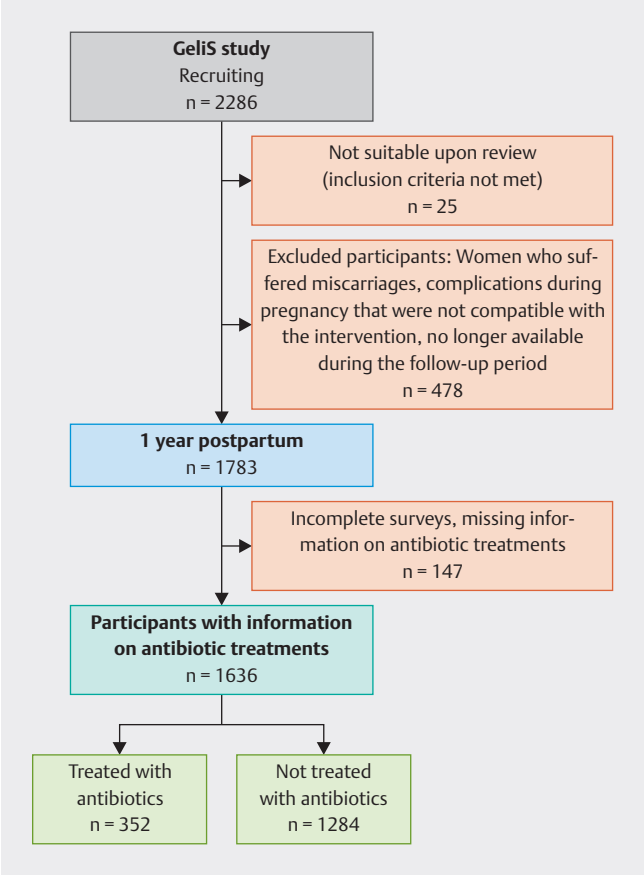
With regard to the breastfeeding behavior of the participants, women who reported breastfeeding their child at least once were referred to as breastfeeding. The precise data collection and analysis of the breastfeeding data from the GeliS study were described by Hoffmann et al. [27]. All data were entered into the central database of the GeliS study at the Munich Study Center. Prior to final evaluation, the plausibility and quality of the data sets were checked according to established standards.

Data processing and statistical analysis

The analysis is based on the data from all study participants who participated in the 1-year follow-up and provided complete information on antibiotic treatment. The information on antibiotic therapies was described depending on the treatment reasons and active ingredients used by frequency distributions during pregnancy and in the first six months postpartum. A possible influence of the intervention on the frequency of treatment was examined using a chi-square test.

Subsequently, the treatment frequencies were analyzed depending on other potential influencing factors. For this purpose, the indication of completed antibiotic treatment was determined as a target variable. First, we investigated possible differences between the intervention and control groups using generalized estimating equations [28]. Various covariates were used, such as educational level, smoking status, partnership, breastfeeding behavior, type of delivery (caesarean section or vaginal birth), and premature birth (before the 37th week of pregnancy). The model was adjusted for the variables parity, as well as the age and BMI category prior to pregnancy. Logistic regression was chosen to model the binary target variable antibiotic therapy yes/no (1/0). In order to account for regional differences, the regions were used as a subject variable, which were distributed over five administrative regions. During cluster randomization in the GeliS study, two regions with similar birth figures and sociodemographic characteristics were selected within each administrative region (Upper Bavaria, Upper Palatinate, Upper Franconia, Middle Franconia, and Lower Franconia) and randomly defined as either a control or intervention region. IBM SPSS for Windows (Version 26.0 IBM Corp., Armonk, NY, USA) was used as the statistics program. All coefficients whose P values were below 0.05 were considered statistically significant.

In order to check how well the information on antibiotic therapies corresponded to the currently valid recommendations, the Embryotox Portal of the Pharmacovigilance and Consultation Center for Embryonic Toxicology at the Charité University Medical Center of Berlin [15] was used as a main reference. Indicators of the quality of treatment were the reasons for treatment, the appropriateness of the preparations, and attention to particularly vulnerable phases during pregnancy. All preparations mentioned



▶ **Fig. 1** Flow chart on the inclusion of the study participants with information on antibiotic treatments.

by the study participants were compared with the recommendations in Embryotox [15] as well as the currently valid guidelines [16, 17, 18, 19] on antibiotic therapy during pregnancy. In addition, recommendations were specifically researched at different times of treatments during pregnancy and breastfeeding, e.g., during particularly vulnerable phases [14] in order to be able to evaluate the treatment frequencies at different times during pregnancy and postpartum.

Results

Participants and their characteristics

Of the 2286 women included in the GeliS study, information on antibiotic treatment during pregnancy and in the first six months postpartum (▶ **Fig. 1**) was available for 71.6% of participants (n = 1636).

The mean age of the women included in the evaluation was 30.5 ± 4.3 (standard deviation) years (▶ **Table 1**). The mean BMI and mean weight prior to pregnancy were 24.3 ± 4.4 kg/m^2 and 68.1 ± 13.2 kg. 44.2% of the women had earned university entrance qualification or had a university degree, while the remaining participants had an intermediate secondary school diploma, lower secondary school diploma or no school diploma. Women who reported antibiotic treatment were more likely to be in the lifestyle intervention group (p = 0.025), were more likely to live without a partner (p = 0.010), and had premature births (p = 0.02) or caesarean sections (< 0.001) more frequently (▶ **Table 1**).

Antibiotic therapies during and after pregnancy

In the GeliS study, 21.5% of women reported a treatment with antibiotics at least once during pregnancy or in the first six months postpartum (▶ **Table 2**). A total of 352 participants received 463 antibiotic therapies, as a proportion of these women were repeatedly treated with antibiotics for recurring infection. Single treatments were the most common (n = 267; 16.3%). Two treatments were performed in 64 women (3.9%), and only 20 women (1.2%) received three or more treatments with antibiotics.

Frequencies of antibiotic treatment over time

The information on the time of antibiotic therapy shows an increasing frequency of treatment from the onset of pregnancy to the first six months postpartum (▶ **Table 2**). Antibiotic treatment occurred in 1.7% of study participants in the first trimester of pregnancy. The relative frequency in the second trimester increased to 5.5%, and in the last trimester it increased to 6.5%. Approximately 7.0% of women were treated with antibiotics in the first six months after birth.

The division of participants into IG and CG showed that pregnant women in the IG were treated with antibiotics significantly more often than in the CG (p = 0.025) (▶ **Table 2**).

Reasons for antibiotic treatment

In 427 out of 463 (92.2%) cases of antibiotic treatment, information about the reason for the treatment was provided. The frequency distributions for antibiotic treatment in ▶ **Fig. 2** refer to data from study participants for whom information on the reasons and associated time was available (n = 410 corresponds to 100%).

Urinary tract infections (n = 119; 28.6% of the reasons; 7.3% of all study participants) were stated as the most common reason for the treatment, with 16 mentions (3.9% of the reasons) of ascending urinary tract infections, mostly pyelonephritis. The occurrence of urinary tract infections was evenly distributed over the different time periods. In 74 cases (18.0% of the reasons; 4.5% of all study participants), other causes were the second most frequently mentioned treatment category. These included, e.g., other bacterial infections (including chlamydia, borrelia), perioperative infection prophylaxis, nonspecific increases in inflammatory parameters, or local inflammation. Compared with the first trimester (1.4% of the reasons), their frequency tripled (second trimester; 4.1%), quadrupled (third trimester; 5.6%) and quintupled (in the first six months postpartum; 6.8%) over time. The third most common were ENT infections, such as otitis media, sinusitis and tonsillitis (n = 59; 14.4% of the reasons; 3.6% of all study participants). Antibiotic treatments for premature rupture of membranes, wound healing disorders after a caesarean section, or birth injuries were classified as birth complications (n = 43; 10.5% of the reasons; 2.6% of all study participants). In the first six months after birth, mastitis (n = 37; 9.0% of the reasons; 2.3% of all study participants) was the most common reason for antibiotic treatment (▶ **Fig. 2** a).

▶**Table 1** Characteristics of the study participants.

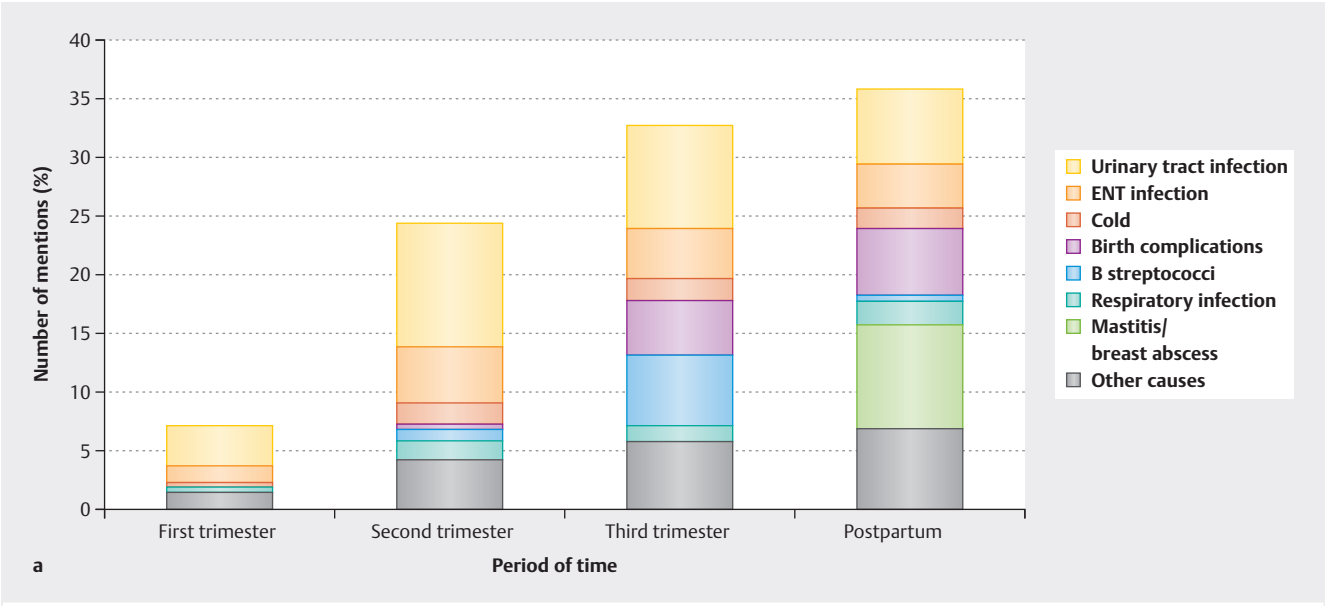
Antibiotic treatment	**Yes** (n = 352)	**No** (n = 1284)	**Total** (n = 1636)	**P value**[b]
Age at study inclusion[a]	30.3 ± 4.3	30.6 ± 4.3	30.5 ± 4.3	0.343
Weight prior to pregnancy (kg)[a]	68.2 ± 13.8	68.1 ± 13.1	68.1 ± 13.2	0.697
BMI prior to pregnancy (kg/m^2)[a]	24.3 ± 4.7	24.3 ± 4.4	24.3 ± 4.4	0.731
BMI category prior to pregnancy [n (%)]				**0.797**
BMI 18.5–24.9 kg/m^2	231/352 (65.6%)	839/1284 (65.3%)	1070/1636 (65.4%)	
BMI 25.0–29.9 kg/m^2	76/352 (21.6%)	294/1284 (22.9%)	370/1636 (22.6%)	
BMI 30.0–40.0 kg/m^2	45/352 (12.8%)	151/1284 (11.8%)	196/1636 (11.9%)	
Weight gain during pregnancy (kg)[a]	13.8 ± 5.2	14.1 ± 5.1	14.0 ± 5.1	0.506
Country of birth [n (%)]				**0.405**
Germany	344/352 (97.7%)	1243/1283 (83.8%)	1587/1635 (97.1%)	
Other country of birth	8/352 (0.23%)	40/1283 (3.1%)	48/1635 (2.9%)	
Level of education, [n (%)]				**0.106**
Lower secondary school diploma/no diploma	38/352 (10.8%)	180/1282 (14.0%)	218/1634 (13.3%)	
Intermediate secondary school diploma	165/352 (46.9%)	530/1282 (41.3%)	695/1634 (42.5%)	
University entrance qualification/university degree	149/352 (42.3%)	573/1282 (44.7%)	722/1634 (44.2%)	
Lifestyle intervention received [n (%)]	197/352 (56.0%)	632/1284 (49.2%)	829/1636 (50.7%)	0.025
Living with their partner [n (%)]	333/352 (94.6%)	1246/1280 (97.3%)	1579/1632 (96.8%)	0.010
Primiparous, [n (%)]	220/352 (62.5%)	765/1284 (59.6%)	985/1636 (60.2%)	0.321
Breastfed child [n (%)]	308/350 (88.0%)	1072/1275 (84.1%)	1380/1625 (84.9%)	0.069
Premature birth [n (%)]	34/352 (9.7%)	66/1281 (5.2%)	100/1633 (6.1%)	0.002
Caesarean section [n (%)]	124/352 (35.2%)	331/1282 (25.8%)	455/1634 (27.8%)	< 0.001

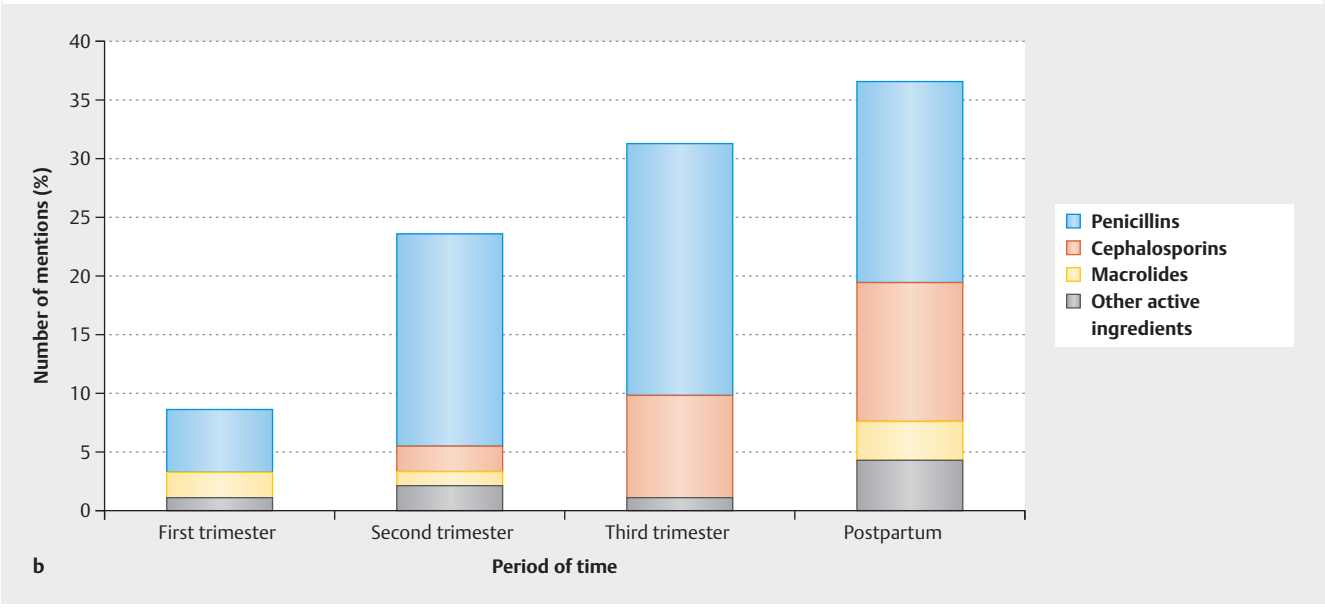
BMI = body mass index.
[a] mean value ± standard deviation.
[b] P value for differences between study participants who were and were not treated with antibiotics, tested using a Kruskal-Wallis test for continuous and a chi-square test for categorical variables.

▶**Table 2** Frequency of antibiotic treatments during pregnancy and in the first six months postpartum.

	Intervention group (n = 829)	**Control group** (n = 807)	**Total** (n = 1636)
Treatment with antibiotics[a] [n (%)]	197/829 (23.8%)	155/807 (19.2%)	352/1636 (21.5%)
First trimester	15/829 (1.8%)	13/807 (1.6%)	28/1636 (1.7%)
Second trimester	51/829 (6.2%)	40/807 (5.0%)	91/1636 (5.6%)
Third trimester	56/829 (6.8%)	50/807 (6.2%)	106/1636 (6.5%)
Six months postpartum	67/829 (8.1%)	48/807 (5.9%)	115/1636 (7.0%)
Child not breastfed	6/127 (4.7%)	4/118 (3.4%)	10/245 (4.1%)
Child breastfed	61/697 (8.8%)	43/683 (6.3%)	104/1380 (7.5%)
IG vs. CG[b]	$X^2 = 5.03$; df = 1; p = 0.025		

[a] The sum of treatments over the observation periods deviates from the total treatments, as data were not available for 12 antibiotic treatments at the time.
[b] Chi-square test based on yes/no information on antibiotic treatments (yes: at least one treatment).





▶ **Fig. 2** Frequencies, reasons (**a**) and active ingredients (**b**) of antibiotic treatments during pregnancy and in the first six months postpartum. When interpreting the illustration, it must be noted that the postpartum period of six months is cumulatively longer than the individual trimesters of pregnancy, and thus the probability of antibiotic treatment increases.

Active ingredients used

Penicillins, including amoxicillin, ampicillin, as well as cephalosporins, erythromycin, and azithromycin (both from the group of macrolides) have been evaluated as safe active ingredients in pregnancy and while breastfeeding [5, 15, 29]. In contrast, the agents in the group of tetracyclines, aminoglycosides, and fluoroquinolones are considered unsafe [15, 29]. In total, only 99 statements on the type of antibiotic preparation could be obtained (20% of the treatments). In the group of penicillins (n = 58), amoxicillin (n = 39) was mentioned the most frequently, including the combination of amoxicillin and the beta-lactamase inhibitor clavulanic acid (n = 1; in the first trimester due to a bacterial infection). In second place were prescriptions of cephalosporins, which, like penicillins, belong to the group of beta-lactam antibiotics (n = 21). In four cases, the information provided related to preparations with less extensive studies, which were subject to a strict risk-benefit assessment but were also considered safe. These included fosfomycin (n = 3) and clindamycin (n = 1) [15].

During pregnancy and postpartum, the proportion of treatments with amoxicillin decreased in favor of other active ingredients (▶ **Fig. 2b**). In the third trimester and postpartum period, cephalosporins were more frequently mentioned (▶ **Fig. 2b**). The information on the active ingredients was distributed very unevenly between the various indications due to incomplete answers. Most of the information on the active ingredients was available for ENT infections, with the beta-lactam antibiotics amoxicillin

and penicillin being most frequently mentioned. Amoxicillin was also frequently used in respiratory or urinary tract infections. In the case of further reasons for administrating antibiotics, no clearly dominant active ingredients could be identified.

A review of the active ingredients mentioned by the study participants (▶ **Fig. 2b**) using the Embryotox database showed that the information on the preparations mentioned in our study corresponded to the current general recommendations.

Possible factors influencing antibiotic therapy

▶ **Table 3** shows the influence of various factors on the frequency of antibiotic treatments in a multivariable model. With 19.5%, fewer participants in the CG received treatment with antibiotic preparations than in the IG (24.0%) ($p < 0.001$; ▶ **Table 2**). Study participants without a partner were treated with antibiotics more frequently than those with a partner ($p < 0.001$). Women who were breastfeeding their children were also treated with antibiotics more frequently compared to non-breastfeeding participants (22.4% vs. 17.1%; $p = 0.008$). Mothers who gave birth to their children vaginally (19.5%) received antibiotics less frequently ($p = 0.003$) compared to mothers who gave birth by caesarean section (27.8%). Antibiotics were used more frequently in premature births ($p = 0.012$). There were no significant changes in treatment rates with regard to level of education or smoking behavior (▶ **Table 3**). Other lifestyle factors, such as a healthy diet, recorded using the Healthy Eating Index (HEI, $p = 0.132$), a vegetarian diet ($p = 0.905$) or physical activity ($p = 0.465$) did not result in any significant changes with regard to the frequency of antibiotic therapies. In a subgroup analysis, participants with caesarean sections were excluded in order to avoid a possible bias due to perioperative antibiotic surgical prophylaxis. In this analysis, there was still a significant increase in the rate of treatment with antibiotics in the intervention group ($p = 0.025$) and in women without a partner ($p < 0.001$) or who breastfed their children ($p = 0.005$), but no longer in women with premature births ($p = 0.113$). The BMI category, age, and parity of women did not affect antibiotic intake.

When dividing the analysis period into pregnancy (model a) and the first six months postpartum (model b), there was little change with regard to the influence of the factors lifestyle advice, living with and without a partner, and smoking behavior (▶ **Table 4** in the attachment). With regard to breastfeeding, the power of the effect (relatively more frequent indication of treatment) was greater compared to the original model (▶ **Table 3**), but the variable lost significance. The variables type of delivery and premature birth were significant depending on how the participants assigned the treatment to the third trimester or the first six months postpartum (▶ **Table 4**).

Discussion

In our study cohort, approximately one in five women was treated with an antibiotic during pregnancy or in the first 6 months after delivery. Overall, the results show a cautious attitude of the attending physicians with regard to prescribing antibiotics. This refers to the choice of active ingredients and the low use of antibiotic preparations in the first trimester of pregnancy.

Few studies to date have investigated a trimester-specific frequency of antibiotic treatment during pregnancy [30, 31]. Mensah et al. [30] reported an increase in antibiotic treatment during pregnancy, especially in the third trimester (79.0% of treatments) in Ghana. In contrast, in a Danish cohort of 706 pregnant women, Stokholm et al. [31] described antibiotic prescription frequencies ranging from 13% in the first trimester to 18% in the third trimester. The data from the GeliS study show that antibiotics were used rarely (1.7% of respondents), especially in the first trimester of pregnancy. It cannot deduce from our data whether this is a consideration of the treating physicians of the particularly vulnerable developmental phase of the embryo during the first trimester of pregnancy [5, 31, 32]. It is well known that the frequency of certain infections increases during the course of pregnancy and, accordingly, an increase in the frequency of treatment is plausible [32].

The main indication for antibiotic treatment are bacterial infections and infection prophylaxis measures [3]. However, there is a high degree of interindividual variability in the frequency of treatment. While Bookstaver et al. [5] reported a treatment prevalence of 20–25% in pregnancy (based on studies from Finland, Canada, and the Netherlands), a frequency of 65% was found in pregnant women in Ghana [30]. The most common reason for antibiotic treatment in the GeliS study was urinary tract infection (7.3% of all study participants). These figures correspond to the frequencies of 2–7% [33] or 5–10% [34] of urinary tract infections treated with antibiotics during pregnancy from other studies. Of particular note are infections or asymptomatic colonization with group B streptococci, which should be treated to prevent B streptococci sepsis in newborns [35]. According to an analysis by Kwatra et al. [36], these have a prevalence of approximately 19% in Europe. In our study, just under 2% of women reported an infection or colonization with group B streptococci. Since this was self-reported, this information may also be substantially too low.

For antibiotic therapies of bacterial infections in pregnancy and breastfeeding, the group of penicillins and cephalosporins is considered particularly suitable [29]. The antibiotic most commonly used for treatment in the GeliS study was amoxicillin. There are well-established studies for this broad-spectrum penicillin and it appears to be safe in pregnancy and breastfeeding [37]. Furthermore, as recommended for pregnancy [15], first and second-generation cephalosporins were used for treatment. Like penicillins, these belong to the group of beta-lactam antibiotics [5, 38]. The remaining antibiotic preparations were ampicillin, fosfomycin, various macrolides (e.g., erythromycin and azithromycin), and other individual active ingredients that are considered unproblematic or safe in pregnancy and breastfeeding [15]. However, with the use of e.g., clavulanic acid, health risks cannot be ruled out [5].

▶**Table 3** Possible factors influencing treatment with antibiotics (multivariable model).

	n (treatments/ participants)	Percentage	Effect size (95% CI) [Odds Ratio]	P value[a]
Group affiliation				
Control group	155/798	19.5%	Reference	
Intervention group	197/820	24.0%	1.32 (1.22–1.42)	< 0.001
Level of education				**0.092**
Lower secondary school diploma/no diploma	38/214	17.8%	Reference	
Intermediate secondary school diploma	156/686	22.7%	1.40 (0.96–2.06)	0.083
University entrance qualification/university degree	149/718	20.8%	1.11 (0.79–1.57)	0.549
Partner				
No partner	19/53	35.8%	Reference	
Partner	330/1565	21.1%	0.44 (0.27–0.70)	< 0.001
Smoking behavior				
Non-smoker	318/1412	22.5%	Reference	
Smoker[b]	34/206	16.5%	0.64 (0.37–1.13)	0.123
Breastfeeding behavior				
Child not breastfed	42/245	17.1%	Reference	
Child breastfed	308/1373	22.4%	1.52 (1.13–2.04)	0.005
Type of delivery				
Vaginal birth	228/1172	19.5%	Reference	
Caesarean section	124/446	27.8%	1.61 (1.18–2.21)	0.003
Premature birth[c]				
No	218/1518	14.4%	Reference	
Yes	34/100	34.0%	1.94 (1.16–3.26)	0.012

BMI = body mass index; CI = confidence interval.
[a] Logistic regression function in a generalized estimating equation (GEE) model adjusted for parity, age, and BMI category prior to pregnancy. P values for Wald-chi-square test.
[b] Smoking during pregnancy and/or up to one year postpartum.
[c] Birth before the 37 th completed gestational week

The frequency of antibiotic treatment also depends on a number of patient-specific influencing factors, such as level of education, income, age, sociocultural status, or lifestyle habits [3, 21, 31, 39]. In contrast to the studies by Stokholm et al. [31] and Mangrio et al. [39], which described the influences of level of education, age, parity, and other sociodemographic factors on the frequency of antibiotic treatment, our study showed only trends but hardly any significant effects. Education, age, smoking status, or parity did not show any significant influence on treatment with antibiotics. Participants without a partner were significantly more likely to be treated with antibiotics in our study, which could be explained by a lack of social support [39]. In contrast, women who were breastfeeding their children received antibiotics more frequently, which is likely to be due to the increased incidence of breast inflammation as a result of breastfeeding [40]. It should be noted that breast inflammation and abscesses were less frequent in the intervention group than in the control group. This difference could be explained by the more thorough discussion of breastfeeding by the GeliS counselling staff in the intervention group. In addition, a caesarean section was associated with a significantly increased probability of receiving antibiotics. This can be explained by routine antibiotic prophylaxis during surgical procedures [41]. Antibiotics were also used significantly more frequently with babies born prematurely, which seems plausible, as surgical deliveries by caesarean section may occur more frequently or the premature birth itself may also be an indication for maternal antibiotic prophylaxis. This was also confirmed in a subgroup analysis of our study. After excluding caesarean sections, there was no significant increase in the frequency of antibiotic treatment for premature births. In addition, increasing intrauterine infections or premature rupture of membranes may promote premature births, which is why antibiotics should be administered prophylactically in this context [42].

In our analysis, a significant effect of GeliS lifestyle counseling on the probability of antibiotic treatment was also observed. Therefore, various other variables relating to lifestyle, such as

nutritional quality (via the "Healthy Eating Index"), a vegetarian diet, or exercise and sports habits were investigated in order to classify the effect of intervention in as much detail as possible. However, these factors did not show any significant influence on the use of antibiotics.

The significantly increased frequency of antibiotic treatment in the IG may be due to study participants being more aware of health issues and leading a more health-conscious lifestyle, associated with more intensive medical consultations. In particular, infection prophylaxis measures were performed more frequently in the intervention group compared to the CG. Thus, intensive lifestyle counseling does not appear to reduce the frequency of antibiotic treatments contrary to expectations. This finding requires further analysis. Overall, the results of this and other studies suggest that the current knowledge about the frequency of infections and their antibiotic treatment, as well as relevant influencing factors, is still very limited. At the same time, a careful risk-benefit assessment remains important in order to adequately treat patients and to avoid excessive use of antibiotics due to the known risks and development of resistant bacterial strains [3].

The sample size of 1636 women surveyed is very helpful in gaining an insight into the regional reality of care. However, there was no systematic survey of a total cohort of pregnant and breastfeeding women for a specific period of time and in a defined area of care, but rather an open survey that was carried out within a selected study population. Thus, generalization to the entire population of pregnant women over a cross-regional or national scale is only limited. Another limitation of this analysis is that the data on antibiotic treatment were collected retrospectively using surveys. Thus, memory bias cannot be ruled out, especially regarding the information on the preparations, but also on antibiotic treatments during the birth. In addition, these data were exclusively self-reported by the participants, which is likely to further limit the validity of the data. The low mentioning of treatments, especially in the peripartum phase, e.g., in caesarean sections, indicate underreporting, as according to the guideline, antibiotic prophylaxis should be administered at every caesarean section and also for premature births for certain indications [41, 42]. However, it is unclear how consistently this recommendation is being implemented. A possible spatial correlation of treatment frequencies due to the cluster structure of the study was factored in by appropriately taking this structure into account in the context of the generalized estimation equations.

The strengths of this study are the sample size, the analysis of numerous possible influencing factors, and detailed information on antibiotic treatment during pregnancy and in the first six months postpartum, e.g., about the respective reasons for treatment, prescribed preparations, and the timing and frequency of treatments.

Conclusion

The results of our analysis show that antibiotic treatment is administered during pregnancy and postpartum in approximately one in five women, comparable to the results from other European countries. The information provided by the study participants on the antibiotic preparations used corresponds to the current treatment recommendations. Individual factors such as sociodemographic parameters, lifestyle, and pregnancy counseling may well be relevant when antibiotics are used. However, there is still a lack of robust evidence on this issue, so further studies are required before counseling and treatment of pregnant and breastfeeding women regarding antibiotic therapies can be specifically improved. Based on the experience from our analysis, it is advisable for future studies to also include the physicians in the data collection. Underreporting during the peripartum phase could also be an indication of a lack of patient information about antibiotic treatment during and shortly after birth. This is a starting point for improving current medical practice. In addition, the creation of antibiograms, especially in the case of multiple treatments, can improve the detection of resistant bacterial strains.

Attachment

(▶ **Table 4**)

▶**Table 4** Possible factors influencing treatment with antibiotics (multivariable models).

	Pregnancy (model a)			Postpartum (first 6 months) (model b)		
	n (treatments/ participants) [%]	**Effect size (95% CI)** [Odds Ratio]	**P value[a]**	**n (treatments/ participants)** [%]	**Effect size (95% CI)** [Odds Ratio]	**P value[a]**
Group affiliation						
Control group	103/804 [12.8]	Reference		48/798 [6.0]	Reference	
Intervention group	122/823 [14.8]	1.21 (1.03–1.42)	0.021	67/820 [8.2]	1.38 (1.02–1.87)	0.036
Level of education			**0.214**			**0.003**
Lower secondary school diploma/ no diploma	29/217 [13.4]	Reference		7/214 [3.3]	Reference	
Intermediate secondary school diploma	110/692 [15.9]	1.28 (0.84–1.94)	0.254	53/686 [7.7]	2.20 (1.35–3.61)	0.002
University entrance qualification/ university degree	86/718 [12.0]	0.94 (0.69–1.30)	0.717	55/718 [7.7]	2.06 (0.84–5.02)	0.113
Partner						
No partner	13/53 [24.5]	Reference		6/53 [11.3]	Reference	
Partner	212/1574 [13.5]	0.45 (0.22–0.91)	0.027	109/1565 [7.0]	0.59 (0.34–1.05)	0.073
Smoking behavior						
Non-smoker	211/1551 [13.6]	Reference		102/1412 [7.2]	Reference	
Smoker	14/76 [18.4]	1.20 (0.80–1.79)	0.382[b]	13/206 [6.3]	0.87 (0.48–1.58)	0.649[c]
Breastfeeding behavior						
Child not breastfed	–	–	–	10/245 [4.1]	Reference	
Child breastfed	–	–	–	104/1373 [7.6]	1.92 (0.89–4.14)	0.098
Type of delivery						
Vaginal birth	158/1176 [13.4]	Reference		60/1172 [5.1]	Reference	
Caesarean section	67/451 [14.9]	1.09 (0.77–1.54)	0.619	55/446 [12.3]	2.74 (1.77–4.23)	< 0.001
Premature birth[d]						
No	200/1527 [13.1]	Reference		107/1518 [7.0]	Reference	
Yes	25/100 [25.0]	2.24 (1.20–4.20)	0.012	8/100 [8.0]	1.04 (0.49–2.19)	0.921

BMI = body mass index; CI = confidence interval

(a) and (b) The models differ in terms of the time periods included (a: pregnancy, b: first 6 months postpartum) and the variable on breastfeeding behavior.

[a] Logistic regression function in a generalized estimating equation (GEE) model adjusted for parity, age, and BMI category prior to pregnancy. P values for Wald-chi-square test.

[b] Smoking during pregnancy.

[c] Smoking during pregnancy and/or up to one year postpartum.

[d] Birth before the 37 th completed gestational week.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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