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Increasing use of antibiotics in pregnancy during the period 2000–2010: prevalence, timing, category, and demographics

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Objective The aim of this study was to describe the use of antibiotics in a national population-based cohort of pregnant Danish women between 2000 and 2010.

Design Register-based, population-wide, cohort study.

Setting Denmark, from 2000 to 2010.

Population All pregnancies among Danish residents during the period 2000–2010 were included for analysis.

Methods Data were obtained from the Danish Medical Birth Registry, the Danish National Patient Registry, and the Registry of Medicinal Product Statistics. The filled prescriptions for systemic antibacterial, antimycotic, and antiviral drugs, as well as intravaginally applied antibiotics, were analysed. Associations with demographic variables were assessed using multivariate analysis.

Main outcome measures Filled prescriptions for antibiotic drugs during pregnancy.

Results We included 987 973 pregnancies in Denmark from 2000 to 2010; 38.9% of women with a delivery and 14.8% of women with a miscarriage or termination of pregnancy had one or more antibiotic treatments during pregnancy. Systemic antibacterial drugs were the most frequently used drug group, with filled prescriptions for 33.4% of all deliveries and 12.6% of all abortions. This proportion increased from 28.4% in 2000 to 37.0% in 2010 among deliveries. The biggest change was seen for pivmecillinam, which increased among deliveries from 6.3% in 2000 to 19.5% in 2010. Obese (odds ratio 1.51; 95% CI 1.47–1.56), young (odds ratio 1.35; 95% CI 1.30–1.39), and low-educated women (odds ratio 1.37; 95% CI 1.35–1.1.39) tended to fill more prescriptions of antibiotics during pregnancy.

Conclusions Overall, the number of women who filled prescriptions of antibiotics increased during the 11-year study period. In 2010, at least 41.5% of all deliveries were exposed to antibiotic therapy during pregnancy.

Keywords Antibacterials, antibiotics, antimycotic drug use, Denmark, pregnancy.

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Introduction

During the last decade there has been an increase in antibiotic use across the European Union, although with considerable variation between countries.[1] There are concerns that the use of antimicrobials during pregnancy and the perinatal period may lead to adverse outcomes of pregnancy, including miscarriage.[2] Unintended effects on the neonatal microbiome following *in utero*, perinatal, or neonatal exposure to antibiotics leading to permanent pertubations is of considerable concern.[3,4] The human gut hosts numerous species of bacteria, in quantities ten-fold the total number of human cells, and this colonisation is malleable, with the functional significance of the human microbiome being elucidated by the Human Microbiome Project.[5] Dysfunction of the intestinal microbiome has been associated with various diseases.[6] Early exposure to antibiotics has been associated with childhood obesity,[7] asthma and allergy,[8] and obsessive-compulsive disorder.[9] Even though several studies have highlighted the possible negative effects of antimicrobial treatment during pregnancy, the extent of the use of antimicrobials during pregnancy

remains largely unknown. Nordic studies have described certain trends,[10–12] although not on a single substance level. Furthermore, some of these studies only covered one or a few years, and so do not illustrate changes in drug use over time. Finally, these studies apply different definitions for an exposed pregnancy, in relation to the timing of redemption of a prescription, making comparison difficult. Previous Danish studies have used either regional data sources or have not included all antibiotics.[13,14] One Danish study based on national prescription data until mid-2004 does not address changes in prescription patterns, and includes few demographic covariates.[15] Worldwide, a number of studies have been performed, but they were based on maternal recall of drug use,[16] or upon populations of small sample size.[17,18] The purpose of this study was to quantify the overall use, and changes in prescription pattern, of antibiotic drugs in a national setting of all pregnant Danish women in the period 2000–2010.

Methods

We included all pregnancies in Denmark from 2000 to 2010. For these women, we obtained data on all collected prescriptions for selected antibiotics. Data was obtained from three Danish national registries: the Registry of Medicinal Products Statistics, the Danish Medical Birth Registry, and the Danish National Patient Registry.

Data sources

The Danish Medical Birth Registry (MBR) contains data on all deliveries in Denmark, both hospital-based birth and homebirths.[19] From 1997 the registry has primarily been based on the Danish National Patient Registry, but is supplemented with birth reports on homebirths and stillbirths.

To include all pregnancies in Denmark in the given period, we supplemented data from the MBR with data from the Danish National Patient Registry (DNPR) and from the Danish registry of legally induced abortions, which is a subregistry of the DNPR.[20] The DNPR contains data on all hospitalisations in Denmark since 1977 and outpatient visits since 1995. The National Patient Registry provides information on outcome of early pregnancy loss, whether these were terminations of pregnancy, miscarriage, late miscarriage, gestational trophoblastic disease, or ectopic pregnancy. Using the tenth edition of the International Classification of Diseases (ICD–10),[21] we defined miscarriage as women diagnosed with O00–O03 codes before 24 completed weeks of gestation. Termination of pregnancy was defined as women diagnosed with O04–O06 codes.

Prescription data were extracted from the Registry of Medicinal Products Statistics (RMPS),[22] which contains data on all prescription drugs purchased at all Danish pharmacies by Danish citizens since 1995. The registry does not include information on over-the-counter drugs, the indication for treatment, or the dose prescribed. Treatments during hospitalisation are not covered and, accordingly, were not part of this study; however, any hospital-initiated treatment that continued after hospitalisation was recorded and included. Drugs were categorised according to the Anatomic Therapeutic Chemical (ATC) code established by the World Health Organization (WHO) for the purpose of drug use statistics.[23] Since 1968, each Danish resident has been assigned with a unique personal identification number, which was used to link the different data sources.[24] All linkages were performed within Statistics Denmark, a government institution that collects and maintains electronic records for a broad spectrum of statistical and scientific purposes.[22,25]

Study drugs

We selected 47 different antibiotics from four main ATC groups: J01, systemic antibacterials; J02, systemic antimycotics; J05, systemic antivirals; and G01, locally applied gynaecological anti-infectives and antiseptics. Metronidazole recorded under ATC-code P01AB01 was also included, but was for simplicity reclassified into J01XD01 (also used to denote metronidazole). Antibiotics from the G01 group will be referred to as intravaginally applied drugs. A complete list of the study drugs can be found in Appendix S1.

Pregnancy

All women who had a recorded pregnancy outcome between 1 January 2000 and 31 December 2010, inclusive, were recorded for analysis. We defined the end of pregnancy as the date of delivery or, for miscarriages and terminations of pregnancy, as the date of diagnosis or procedure. A delivery was defined as a livebirth or stillbirth occurring after 24 completed weeks of gestation. Pregnancies ending before 24 completed weeks of gestation was defined as a miscarriage or termination of pregnancy. The start of pregnancy was calculated from the date of delivery or termination minus the recorded length of pregnancy. A normal length pregnancy was defined as 280 days or 40 weeks of gestation,[26] and we defined a trimester to be approximately one-third of the normal gestation period: first trimester, 91 days (up to 13 completed weeks of gestation); second trimester, 98 days (14–26 completed weeks of gestation); third trimester, 91 days (27–40 completed weeks of gestation).

Analysis

To structure the description of the analysis and the presentation of the results, we divided the analysis into four research questions collectively describing the use of antibiotics among pregnant women in Denmark. All analyses were performed using STATA 12.0 (StataCorp, College Station, TX, USA).

What is the prevalence of antibiotic drug use during pregnancy?

We considered a pregnancy as exposed if the mother had collected one or more prescriptions for any study drug at any time during the pregnancy. Prevalence was specified according to each of the four main drug classes and calendar year. We also calculated the average prevalence over the whole study period, specifying maternal age in one-year intervals according to the mother's age at completion of pregnancy.

When during pregnancy did the antibiotic treatment take place?

The distribution of antibiotic drug usage was illustrated by calculating prevalence by trimester for the four main antibiotic groups.

Which antibiotics were used?

We counted the number of times each antibiotic was used, using the fifth level of the ATC system (single substances), specified by trimester. For each of the four main groups, J01, J02, J05, and G01, we listed the prescribed drugs. For each drug, we listed the number of exposed pregnancies and median number of purchases per pregnancy, and the antibiotic prescription prevalence. We illustrated the prevalence according to drug and calendar year for the most commonly used systemic antibacterial drugs and for the intravaginally applied drugs.

Were there any demographic differences between women using antibiotics and non-users?

To illustrate possible differences between women using antibiotics during pregnancy and non-users, we created a table of drug use within a number of demographic subgroups for the overall exposure. The following demographic variables were considered: maternal age (at delivery); pre-pregnancy body mass index (BMI); parity (number of pregnancies of ≥24 completed weeks of pregnancy, including the current pregnancy); highest completed education (low, 7–10 years; middle, 11–12 years; high, 13+ years); mother's nationality; and smoking status at start of pregnancy.

Results

We identified a total of 997 087 pregnancies with a recorded outcome in Denmark between 1 January 2000 and 31 December 2010 (Figure 1). Of these, 9114 pregnancies (<1%) contained no registration of length of gestation and were excluded from the analyses. The remaining 987 973 pregnancies included 696 298 deliveries, 119 125 miscarriages, and 172 550 terminations of pregnancy. In total, 38.9% of women with a recorded delivery and 14.8% of women with a recorded miscarriage or termination of pregnancy had one or more antibiotic treatments during

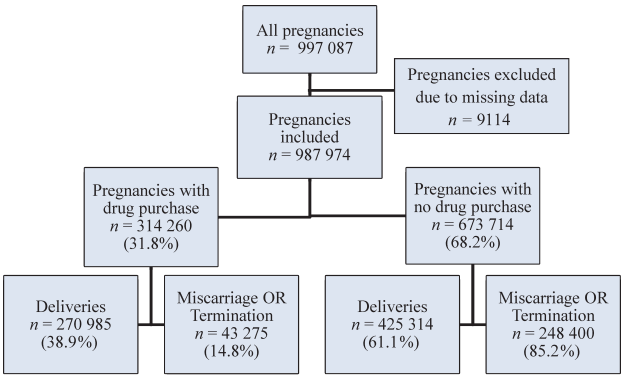

Figure 1. Drug purchases during pregnancy, Denmark, 2000–2010.

pregnancy. The most commonly filled prescriptions for antibiotics during pregnancy among women with a recorded delivery were phenoxymethylpenicillin (ATC, J01CE02), followed by pivmecillinam (ATC, J01CA08) (Table S1), for which prescriptions were filled by 13.8 and 12.4%, respectively. Among miscarriages and terminations of pregnancy, approximately 3.8% filled prescriptions for phenoxymethylpenicillin and 2.4% filled prescriptions for azithromycin (ATC, J01FA10) in the first trimester, compared with 2.3 and 5.5%, respectively, in the second trimester (Table S1). Most prescriptions for systemic antibacterial treatments were filled during the third trimester for deliveries, and second trimester for abortions, whereas prescriptions for intravaginally administered drugs were mainly filled in the second trimester, regardless of the outcome of pregnancy. Prescriptions for systemic antiviral and antimycotic treatments were mainly filled in the first trimester (Table 1).

Using linear regression, we found that prescriptions filled for systemic antibacterial drugs during pregnancy among women with a recorded delivery increased significantly from 2000 to 2010, reaching 37.0% in 2010 ($P < 0.001$). Filled prescriptions for systemic antiviral and antimycotic drugs also increased significantly throughout the study period: prevalence proportion rates for antimycotics changed from 10/1000 to 15/1000, whereas changes for antivirals were from 4/1000 to 14/1000. The prescription prevalence specified by year is shown in Figure 2. Specific age-related prevalence for 2010 is illustrated in Figure S1.

Figure 3 illustrates the trend for women who filled prescriptions for the most commonly used systemic antibacterial drugs and intravaginally applied antibiotics during pregnancy. Filled prescriptions for pivmecillinam among deliveries almost tripled during the study period, from 6.3% in 2000 to 19.5% in 2010 (Figure 3A). The largest relative decrease in filled prescriptions was found for sulfamethizole, clotrimazole, miconazole, and econazole (Figure 3).

Table 1. Antibiotics used during pregnancy by women with a recorded delivery

Antibiotics (Total number of deliveries)	Exposure during pregnancy *n* = 696 298 (%)	Average number of treatments Mean (range)	1st Trimester *n* = 696 298 (%)	2nd Trimester *n* = 696 298 (%)	3rd Trimester *n* = 694 579 (%)
Systemic antibacterials	232 889 (33.4)	1 (1–3)	89 712 (12.9)	102 309 (14.7)	104 136 (15.0)
Systemic antimycotics	7882 (1.1)	1 (1–1)	5883 (0.8)	1306 (0.2)	965 (0.1)
Systemic antivirals	5047 (0.7)	1 (1–2)	2377 (0.3)	1339 (0.2)	2208 (0.3)
Intravaginal antibiotics	61 901 (8.9)	1 (1–2)	16 744 (2.4)	28 750 (4.1)	25 717 (3.7)

Table 2 illustrates the difference in the prevalence proportions of filled prescriptions for antibiotics among women with a recorded delivery according to various demographic parameters. Notably, the proportion of filled prescriptions was higher among women in obese class III (50.4% of women with a pre-pregnancy BMI > 35 kg/m^2), women who were young (49.3% of women below the age of 20 years), and women with low education levels (46.0% of women with an education of 10 years or less). Minor demographic differences were noted for women in obese classes II and III, women of African ethnicity, women with parity > 1, and women who were smokers. Demographic characteristics for miscarriages are listed in Table S2.

Discussion

Main findings

In this population-based study of nearly one million pregnancies over an 11-year period, we have demonstrated that: (1) 38.9% of all deliveries and 14.8% of abortions had filled prescriptions for one or more antibiotic treatments during pregnancy; (2) the most common treatment was with systemic antibacterials, which increased from approximately 28.4% of deliveries in 2000 to 37.0% in 2010; and (3) filled prescriptions for antibiotics varied according to certain demographics. Overall, we found that antibiotic treatment during pregnancy was far more common among deliveries compared with abortions. This was at least in part because of the shorter length of gestation, and therefore lower risk of exposure.

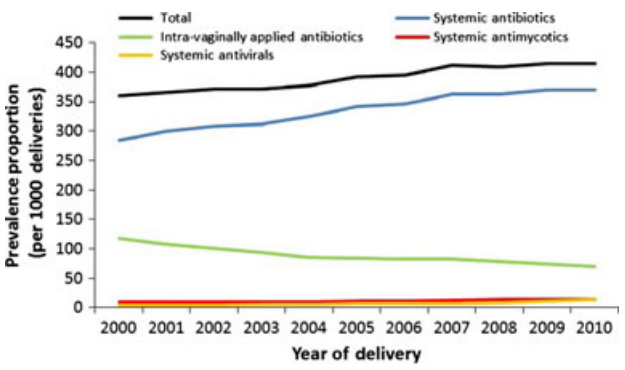

Figure 2. Prevalence of antibiotic drug use during pregnancy by calendar year for the period 2000–2010.

Strengths and limitations

Our study has several strengths: (1) the use of population-based registries reduces selection bias and secures a comprehensive registration of drug use from a well-defined, unselected population;[22] (2) all registered pregnancies in Denmark were included, whether they ended in live birth, stillbirth, miscarriage, or termination of pregnancy; (3) the RMPS has been found to have a very high data coverage and validity;[22] (4) recall bias was eliminated as all data were registered prospectively;[27] and (5) the use of prescription data did not rely on self-reported use.

All but one of the drugs included in the analysis were fully covered by the database; however, around 85% of the overall sale of clotrimazole in 2010 was sold over the counter.[28] This greatly limits any analysis made on the use of this drug. A possible explanation for this distribution could be that over-the-counter sales are cheaper for the patient; however, both the overall sale of clotrimazole and the proportion of these sales sold on prescription decreased from 2001 to 2010.[28]

The main limitation to this study is that we only have information on prescription drugs from outpatient pharmacies. Severe infections are likely to be treated in hospital and therefore not covered by our analyses. Another limitation is that we used collected prescriptions as a proxy for the patients actually taking the drug, potentially leading to an overestimation of antibiotic use during pregnancy.[29] It is also assumed that prescriptions filled during a specific trimester correspond to actual medication use in the given trimester.

Interpretation

Our findings were similar to those in other Nordic countries. From 1996 to 2006, 27% of all deliveries in Finland were prescribed systemic antibacterials, 6.8% were prescribed intravaginally applied antibiotics, and 1.3% were

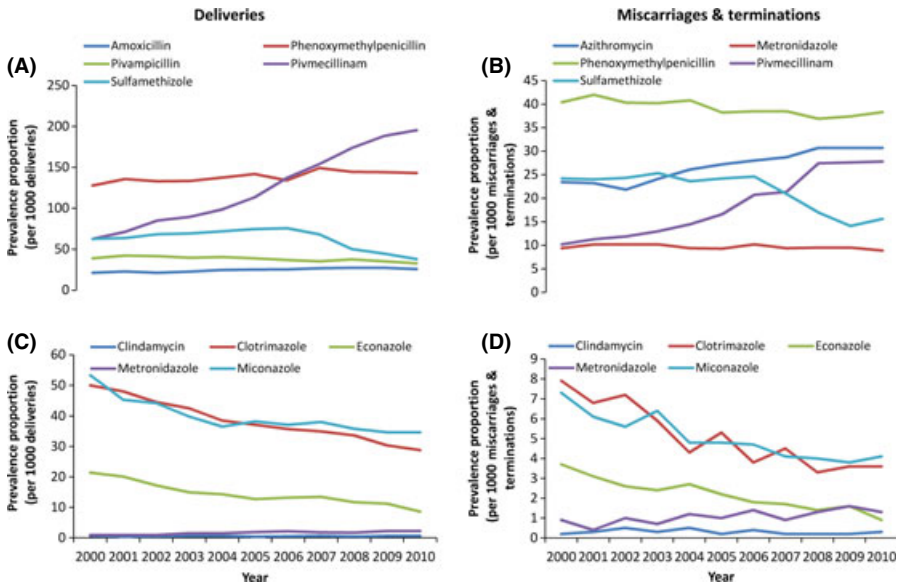

Figure 3. Prevalence of systemic antibacterials and intravaginally applied antibiotics used during pregnancy by calendar year for the period 2000–2010. (A) Systemic Antibacterials among deliveries. (B) Systemic Antibacterials among miscarriages & terminations. (C) Intravaginally appliedantibiotics among deliveries. (D) Intravaginally applied antibiotic among miscarriages & terminations.

prescribed systemic antimycotics.[12] In Norway, the prevalence of systemic antibacterials (2004–2006) was 42.5% and the prevalence of intravaginally applied antibiotics was 4.1%; however, these findings covered a period from 3 months prior to the pregnancy until 3 months after delivery.[10] In addition, their overall estimate of the incidental prescription of systemic antibacterials was higher than ours, whereas their findings by trimester were slightly lower than ours. Similar results were found in a Swedish study in 2007.[11] A Danish study found that 29% of singleton pregnancies were prescribed antibiotic treatment during pregnancy;[30] however, that study was limited to the northern and the central regions of Denmark, and only included singletons who survived >29 days following delivery. In another study of population-wide Danish national prescription data from 1996 until mid-2004, about 31% of women giving birth to liveborn singletons were prescribed an antibiotic, confirming our finding of an increased prescription rate.[15] Other studies from Germany, the USA, and the UK, based on selected populations, lacked information on pregnancy length or only described antibiotics at the second ATC level.[31–33]

There are differences in the management of infections in pregnancy versus infections in non-pregnant women because of pregnancy-associated physiological changes, and the possible effect of an infection and its treatment on the fetus.[34]

We found that the timing of treatment during pregnancy varied not only between the four main ATC groups but also within each ATC group of antibiotics. Overall, filled prescriptions for systemic antibacterials were most common late in pregnancy; however, the first-choice treatment for airway infections (phenoxymethylpenicillin) was fairly stable throughout pregnancy.

Another common indication for antibiotic drug prescription during pregnancy is urinary tract infection. Acute cystitis occurs in approximately 1–2% of pregnant women,[35] and asymptomatic bacteriuria occurs in 2–10% of all pregnancies. Of women with untreated bacteriuria, up to 25% will develop acute pyelonephritis,[36] and antibiotic treatment of asymptomatic bacteriuria during pregnancy will reduce the risk of pyelonephritis.[36] The first-choice treatment of urinary tract infection, pivmecillinam (the prodrug for mecillinam), is most common later in pregnancy, which may be explained by the increased risk of urinary tract infection arising from physiological changes such as ureteric dilatation.

In addition, some of our findings may be explained by changes in Danish guidelines and recommendations.[37,38] The online drug information site www.pro.medicin.dk is by far the most commonly used drug information resource by healthcare professionals, especially general practitioners, in Denmark. There were about 63 000 page showings for the *Antibiotic Treatment Guideline* in 2013, mainly from the approximately 4000 practitioners in Denmark (T.M. Reersted pers. comm.). Until 2006, sulphamethizol was the recommended first-choice treatment for urinary tract infection. After 2006, the recommendations changed to pivmecillinam as first choice; however, the use of sulphamethizol during the third trimester was not recommended throughout the study period. The change in recommendations can partly explain the continuous decrease in filled

Table 2. Antibiotic use among demographic subgroups

	Total number of deliveries	OR (95% CI)	Pregnancies with at least one antibiotic treatment (%)
Total deliveries	696 298		38.9
Maternal age group			
<20 years	16 134	1.35 (1.30–1.39)	49.3
20–29 years	346 923	1.00 ref.	39.3
30–39 years	321 189	0.93 (0.92–0.94)	38.0
40+ years	12 052	0.89 (0.86–0.93)	38.3
Pre-pregnancy BMI (kg/m^2)			
<18 underweight	10 617	1.03 (0.99–1.07)	40.9
18–24 normal weight	266 288	1.00 ref.	38.2
25–29 overweight	86 531	1.14 (1.12–1.16)	42.2
30–34 obese class I	32 107	1.30 (1.27–1.33)	46.2
35+ obese classes II & III	16 704	1.51 (1.47–1.56)	50.4
No information	283 815	0.89 (0.88–0.90)	37.0
Parity			
1	304 260	1.00 ref.	35.9
>1	392 038	1.28 (1.27–1.30)	41.3
Nationality			
Danish	598 890	1.00 ref.	38.7
European, non-Danish	43 278	1.01 (0.99–1.03)	39.2
Asian	36 614	1.02 (0.99–1.04)	40.6
African	13 487	1.14 (1.10–1.18)	44.0
South & Central America	2263	1.10 (1.01–1.20)	39.4
North America	1106	0.90 (0.80–1.02)	33.6
No information	660	0.94 (0.80–1.10)	37.6
Education			
Low: 7–10 years	125 667	1.00 ref.	46.0
Medium: 11–12 years	280 456	0.84 (0.83–0.85)	39.5
High: 13+ years	275 872	0.73 (0.72–0.74)	35.3
No information	14 303	0.69 (0.67–0.72)	35.4
Smoking status			
Non-smoker	562 458	1.00 ref.	37.7
Smoker	116 552	1.22 (1.20–1.23)	44.6
No information	17 052	1.09 (1.06–1.13)	40.3

prescriptions for sulphamethizol from 2006. Pivmecillinam has been the recommended treatment of recurring cystitis throughout the study period. Phenoxymethylpenicillin has been the recommended first-choice treatment of upper and lower airway infections throughout the study period. The use of azithromycin during pregnancy was not recommended until 2009 because of a lack of safety data. From 2009, the use of azithromycin during pregnancy has been considered safe.[37] The recommended treatment of chlamydia among non-pregnant women has been azithromycin throughout the study period, whereas the recommended first-choice treatment of chlamydia among pregnant women was erythromycin until 2006, when pivampicillin became the recommended treatment.

The fact that azithromycin is the third most commonly filled prescription antibiotic during pregnancy among abortions may partly be explained by the relatively low prevalence of antibiotic treatments in general among abortions. The trend in filled prescriptions for azithromycin among all pregnancies has been at a constant low level until 2009, when its use during pregnancy changed from 'safety unknown' to 'safe'. This change in recommendation might at least partly explain the slight increase in prevalence proportion among abortions.

Abnormal genital tract flora in early pregnancy is predictive of preterm birth (PTB), so it is logical to consider the use of antibiotics for the prevention of PTB of infectious etiology. Unfortunately, a number of studies have used different diagnostic methods, outcome parameters, definitions of success, risk groups, host susceptibilities (and therefore host response), degrees of abnormal flora, antibiotic dose regimens and routes of administration, and gestational age

at time of treatment. Not surprisingly, this has led to conflicting results. Accordingly, a number of systematic reviews or meta-analyses have been conducted, but none has simultaneously addressed the optimal choice of agent, the choice of patient, and the timing of intervention.[39] These meta-analyses and many of their included studies demonstrate that if inappropriate antibiotics are used in women without evidence of abnormal genital tract flora, and at late gestations, then there is no benefit with respect to the prevention of PTB, except for women with bacterial vaginosis (BV) who are at high risk of PTB. There are concerns however that if these studies are not read carefully they will be cited erroneously as evidence that any antibiotic, given to any pregnant woman, at any gestational age, will be unhelpful in preventing PTB, and for this interpretation, caution has been urged.[40] If antibiotic intervention is to be successful in reducing the incidence of PTB, these antibiotics should: (1) have activity against organisms known to be associated with PTB; (2) be used early in pregnancy before infection/inflammation has had an opportunity to cause irreversible damage, which will inevitably lead to spontaneous preterm labour and PTB; and (3) only be used in women with abnormal genital tract flora. Accordingly, Lamont et al. carried out a systematic review and meta-analysis of clindamycin, an antimicrobial that is active against organisms known to be associated with spontaneous preterm labour and PTB, and that is used in women with abnormal genital tract flora, including BV, in early pregnancy before 22 weeks of gestation.[39] Their hypothesis was that the conclusions of previous individual studies, systematic reviews, and meta-analyses on the use of antibiotics used prophylactically for the prevention of PTB are flawed by the fact that: (1) undue reliance was placed on studies with suboptimal choice of antibiotics (mainly metronidazole); (2) antibiotics were used too late in pregnancy (23–27 weeks of gestation) to influence outcome; and (3) antibiotics were used in women whose risk of PTB was not the result of BV (i.e. risk associated with previous PTB, low BMI, positive fetal fibronectin, or detection of ureaplasmas, group B *streptococcus*, or *Trichomonas*). Conversely, their hypothesis was that antibiotics active against BV-related organisms, used in women whose risk of PTB is associated with abnormal flora, and used early in pregnancy before irreversible inflammatory damage occurs, can reduce the rate of PTB. This systematic review and meta-analysis demonstrated that when clindamycin was administered before 22 weeks of gestation to women with objective evidence of abnormal genital tract flora: (1) the rate of PTB before 37 completed weeks of gestation was reduced by 40%; and (2) late miscarriage was reduced by 80% in women who received clindamycin, compared with controls.

We identified several demographic differences between women who filled prescriptions for antibiotics and non-users. These variations may be explained by obesity being associated with a higher risk of diabetes, and therefore a greater susceptibility to infections, and younger women being more exposed to sexually transmitted infections (STIs), and therefore being at a higher risk of infections. In contrast, a Finnish study found that the frequency of antibiotic drug purchases was higher among women in older maternal age groups and women belonging to a higher socio-economic group.[12]

Conclusion

The proportion of pregnant Danish women who filled prescriptions of antibiotics has increased during the 11-year study period. In 2010, 41.5% of all deliveries filled prescriptions of antibiotics during the pregnancy, and the filled prescription rate of pivmecillinam tripled, to comprise 19.5% of all deliveries during the study period. Our results indicate that the clinical prescription of antibiotics in Denmark appears to be in accordance with clinical guidelines.

Future research should include studies on antibiotic drug prescription during hospitalisation, details on prescription indications, and associations with pregnancy outcome, such as miscarriages, malformations, birthweight, prematurity, small for gestational age, and neonatal adaption, as related to antibiotic exposure.

Disclosure of interests

The authors declare no conflicts of interest.

Contribution to authorship

AB made a substantial contribution to conception and design, acquisition of data, analysis and interpretation of data, drafting and revising of the article, and approved the final version for publication. AP made a substantial contribution to the acquisition of data, analysis and interpretation of data, drafting and revising the article, and approved the final version for publication. RFL made a substantial contribution to conception and design, interpretation of data, critically revising the article, and approved the final version for publication. JSJ made a substantial contribution to conception and design, interpretation of data, critically revising the manuscript, and approved the final version for publication. PD made a substantial contribution to conception and design, acquisition of data, interpretation of data, drafting and revising the article, and approved the final version for publication.

Details of ethics approval

The study was approved by the Danish Data Protection Agency. Approval from the Ethics Committee was not required.

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None.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Prevalence of antibiotic drug users during pregnancy, by age.

Table S1. (a) Antibiotic drugs used during pregnancy among deliveries. (b) Antibiotic drugs used during pregnancy among women with miscarriage or terminated pregnancy.

Table S2. Antibiotic use among demographic subgroups.

Appendix S1. List of study drugs. ■

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