

Use of prescribed drugs among primiparous women: an 11-year population-based study in Denmark

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Purpose: To describe patterns of prescribed drug use over time among primiparous women in Denmark.

Methods: Through the Danish Medical Birth Registry, we identified all primiparous women giving live birth or stillbirth at ≥ 22 gestational weeks in northern Denmark, from 1999 to 2009. From the Aarhus University Prescription Database we obtained information on the women's prescriptions for reimbursed drugs filled from 30 days before conception until delivery.

Results: Among 85,710 primiparous women, 47,982 (56.0%) redeemed at least one prescription from 30 days before conception until delivery. Women aged 35 years and older had the highest overall prevalence of prescription drug use (61.1%). Age-standardized prevalence of drug use was 54.7% in 1999 and 61.2% in 2009, prevalence ratio (PR) of 1.13 (95% confidence interval 1.10; 1.16), adjusted for age and smoking.

Conclusion: Over the 11-year period from 1999 to 2009, we found a modest increase in overall use of drugs by primiparous women in Denmark. This increase was not, however, explained by an increasing proportion of older first-time mothers. We noted changes in patterns of use of anti-infective drugs and antidepressants.

Keywords: drug utilization, epidemiology, pregnancy

Introduction

Reported prevalence of drug use during pregnancy in Western countries ranges from 44% to 99%, and many pregnant women use several different drugs.¹⁻⁷ Because pregnant women are typically excluded from randomized studies of drugs, evidence about drug utilization and safety in pregnant women comes primarily from surveillance.^{8,9}

Despite lack of data on safety, drug therapy during pregnancy is sometimes required to treat maternal conditions.¹⁰ Women in developed countries are delaying childbearing into later reproductive years:¹¹ in Denmark, the prevalence of first-time mothers older than 30 years has increased from 29% in 1997 to 41% in 2007.¹² Temporal changes in demographic, social, or clinical characteristics of pregnant women as well as modifications in treatment guidelines may affect patterns of drug utilization in pregnancy.^{10,13}

Previous studies have mainly reported period prevalence of drug use among pregnant women, and have examined use according to trimester of pregnancy.¹⁻⁷ Little data exist on temporal changes in drug use during pregnancy.^{10,14} In this population-based study, we examined changes in patterns of prescribed drug use from 1999 to 2009 among Danish primiparous women.

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Methods

Study population

In the Danish Medical Birth Registry, we identified all primiparous women (ie, women delivering their first live- or stillborn child at ≥ 22 weeks' gestation)¹⁵ from 1 January 1999 to 31 December 2009 in the Central and the North Denmark Regions, which together comprise about 33% of the total Danish population (1.8 million people). The Medical Birth Registry has recorded all births in Denmark since 1973 and contains data on characteristics of the mother (including age, residence, parity, and self-reported smoking status) and the newborn (including vital status at birth, sex, gestational age, and birth weight).¹⁶ The information on gestational age is based on ultrasound and is recorded in full completed weeks (through 1996) and in fractional weeks (based on days) thereafter.¹⁷ We calculated the conception date as birth date minus gestational age in days plus 14 days.

Identification of prescribed drugs

We obtained information on drug use in pregnancy using the Aarhus University Prescription Database, which tracks prescriptions for reimbursed drugs redeemed at the regions' outpatient pharmacies.¹⁸ The pharmacies use electronic accounting systems to secure reimbursement from the National Health Service. Denmark's tax-supported health care system partially refunds the costs of most prescribed drugs.¹⁹ To secure full prescription records for each pregnancy in the study population, we restricted our study to women who were residents of the two regions from 30 days before conception until delivery and who were therefore assumed to have redeemed their prescriptions in the regions' outpatient pharmacies.

We defined drug use as a record of at least one prescription dispensation recorded in the Aarhus University Prescription Database from 30 days before conception until delivery. For all prescriptions, we noted the woman's personal identifier, date of reimbursement, and type of medication, coded using the Anatomical Therapeutic Chemical (ATC) classification. The Aarhus University Prescription Database does not track in-hospital medicinal treatment. Nonreimbursed drugs (over-the-counter [OTC] preparations, prescription sedatives, hypnotics, or oral contraceptives) are not recorded unless they are approved for reimbursement, eg, to treat a chronic condition.¹⁸

Data linkage

Data were linked using the unique 10-digit personal identifier ("CPR number"), assigned to all Danish residents at

birth by the Civil Registration System since 1968.²⁰ The CPR number, which encodes date of birth and sex, is used in all public records. Maternal CPR number is a variable on the newborn's Medical Birth Registry entry, enabling unambiguous linkage to the maternal prescription record. Furthermore, the Civil Registration System contains a variable encoding residence.

Statistical analyses

We computed prevalence of drug use among primiparous women according to maternal age at delivery (<25 years, 25–29 years, 30–34 years, and ≥ 35 years), smoking during pregnancy (yes/no), and categories corresponding to the major anatomical ATC groups.²¹ We further analyzed six major anatomical ATC groups with prevalence of use in pregnancy exceeding 4%. These groups, listed in the order of decreasing prevalence of use, were: anti-infective drugs for systemic use (ATC group J), gynecological drugs (ATC group G), dermatological drugs (ATC group D), drugs for respiratory diseases (ATC group R), drugs for alimentary tract and metabolism (ATC group A), and neurological drugs (ATC group N). In 1998, clinical guidelines were introduced in Denmark for treatment of asymptomatic urinary tract infections in pregnancy.^{22,23} For anti-infective drugs, we therefore specifically examined prevalence of drug use indicated for urinary tract infections (UTIs) (sulfamethizole (J01EB02), pivmecillinam (J01CA08), and nitrofurantoin (J01XE01)), while examining use of penicillin (phenoxymethylpenicillin (J01CE02), pivampicillin (J01CA02), and amoxicillin (J01CA04)) for comparison. After observing an increasing trend in use of neurological drugs throughout the study period, we did a post-hoc analysis to examine change over time in prevalence of drug use in specific subgroups: antidepressants (N06A), anti-epileptics (N03), and opioids (N02A).

We computed age-standardized prevalence of drug use in each calendar year (1999–2009), with age distribution in year 1999 as the standard. Further, we estimated age- and smoking-adjusted prevalence ratios (PRs) for drug use with corresponding 95% confidence intervals (CIs), using 1999 as the referent year. Furthermore, we tested for presence of a trend across years using the Chi-square test for trend.

We examined patterns of drug use over time within four gestational periods: immediate pre-conception (1–30 days before estimated conception), first trimester (gestational week 1–12), second trimester (gestational week 13–28), and third trimester (gestational week 29 to delivery). We compared pre-conception and trimester-specific

Table 1 Characteristics of primiparous women in Northern Denmark 1999–2009

	All primiparous women (n = 85,710)	Primiparous women who redeemed at least one prescription during pregnancy (n = 47,982)
Age at delivery, years		
<25	18,170 (21.2)	10,637 (22.2)
25–29	39,221 (45.8)	20,824 (43.4)
30–34	21,540 (25.1)	12,382 (25.8)
≥35	6779 (7.9)	4139 (8.6)
Smoking during pregnancy ^a	15,046 (17.6)	9014 (18.8)
Single births	83,405 (97.3)	46,348 (96.6)
Twin births	2256 (2.6)	1593 (3.3)
Triplet births	49 (0.1)	41 (0.1)
Low birth weight ^b (<2500 g)	3975 (4.8) ^c	2309 (5.0) ^c
Preterm birth (<37 weeks)	5550 (6.7) ^c	3217 (6.9) ^c
Stillbirth (≥22 weeks)	362 (0.4) ^c	221 (0.5) ^c

Notes: ^a1826 missing values (2.1%); ^b494 missing values (0.6%); ^cSingleton pregnancies only.

prevalence of drug use in 1999–2000 (the first two years of observation) with that in 2008–2009 (the last two years of observation). Using years 1999–2000 as the reference, we estimated gestational-period specific prevalence ratios for drug use, adjusted for age at delivery and smoking in pregnancy.

All analyses were performed using Stata software 10.0 (College Station, TX). The study was approved by the Danish Data Protection Agency (journal number: 2003-41-3103).

Results

During the study period, we identified 85,710 primiparous women, delivering 88,003 live- or stillborn children. Mean age at delivery was 28 years (range 13–52 years); the proportion of first-time mothers aged 30 years and older increased from 29.0% in 1999 to 35.8% in 2009. Compared with all primiparous women, those with prescription drug use were more likely to be smokers, to have multiple births, and to be older. Prevalence of preterm birth and low birth weight differed slightly among groups (Table 1).

Overall, 47,982 (56.0%) of primiparous women redeemed at least one prescription for a reimbursed drug from 30 days before conception until delivery. Women who redeemed prescriptions, redeemed, on average, 3.2 prescriptions (2.3% of these redeemed >10 prescriptions). Women who used anti-infective drugs redeemed on average 1.6 prescriptions (lowest prescription rate per woman), whereas women who used neurological drugs on average redeemed 4.0 prescriptions (highest prescription rate per woman).

The age-standardized prevalence of drug use increased from 54.7% in 1999 to 61.2% in 2009, PR 1.13 (95% confidence intervals [CI]: 1.10; 1.16); the prevalence decreased slightly in the first two years of observation. The overall prevalence of drug use was 58.5% among women younger

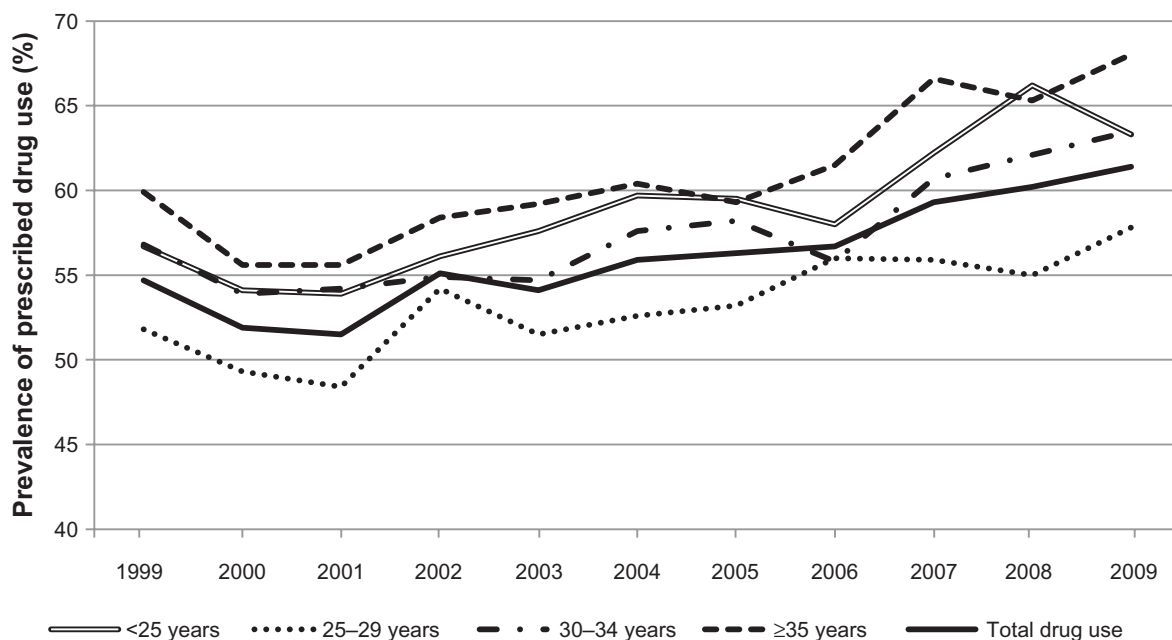


Figure 1 Prevalence of prescribed drug use according to age among primiparous women. Northern Denmark 1999–2009.

Table 2 Age-standardized prevalence of prescribed drug use and prevalence ratios for overall and ATC-specific drug use among primiparous women in Northern Denmark 1999–2009

ATC group	Calendar year of delivery											P-value for linear trend
	1999 (n = 7949)	2000 (n = 8134)	2001 (n = 8031)	2002 (n = 7812)	2003 (n = 8197)	2004 (n = 7956)	2005 (n = 7883)	2006 (n = 7906)	2007 (n = 7745)	2008 (n = 5997)	2009 (n = 8100)	
All ATC groups												
n	4346	4223	4132	4302	4434	4445	4434	4486	4596	3608	4976	P < 0.001
P	54.7	52.0	51.6	55.1	54.3	56.0	56.3	56.8	59.3	60.1	61.2	
PR (95% CI)	I	0.95 (0.92;0.97)	0.94 (0.91;0.97)	1.00 (0.98;1.03)	0.99 (0.96;1.02)	1.02 (0.99;1.05)	1.03 (1.00;1.06)	1.04 (1.01;1.07)	1.09 (1.06;1.12)	1.11 (1.07;1.14)	1.13 (1.10;1.16)	
ATC group A												
n	498	395	305	350	392	392	371	433	518	369	560	P < 0.001
P	6.3	4.9	3.8	4.5	4.8	5.0	4.7	5.4	6.6	6.1	6.8	
PR (95% CI)	I	0.77 (0.68;0.88)	0.62 (0.54;0.71)	0.71 (0.62;0.82)	0.76 (0.67;0.87)	0.80 (0.70;0.91)	0.75 (0.65;0.85)	0.88 (0.77;1.00)	1.07 (0.95;1.20)	0.99 (0.87;1.13)	1.10 (0.98;1.24)	
ATC group D												
n	1058	1040	867	930	889	876	785	844	777	604	766	P < 0.001
P	13.3	12.8	10.8	11.9	10.9	11.0	9.9	10.8	10.1	10.1	9.5	
PR (95% CI)	I	0.95 (0.88;1.03)	0.81 (0.75;0.89)	0.90 (0.83;0.98)	0.81 (0.75;0.89)	0.83 (0.76;0.90)	0.75 (0.69;0.82)	0.81 (0.74;0.88)	0.76 (0.70;0.83)	0.76 (0.69;0.83)	0.71 (0.65;0.78)	
ATC group G												
n	1112	1165	1002	1017	1036	970	1013	914	1,126	981	1,270	P = 0.001
P	14.0	14.3	12.5	12.9	12.5	12.1	12.6	11.3	14.0	15.7	14.9	
PR (95% CI)	I	1.02 (0.94;1.10)	0.89 (0.82;0.97)	0.92 (0.85;0.99)	0.87 (0.81;0.95)	0.85 (0.78;0.92)	0.90 (0.83;0.97)	0.81 (0.74;0.88)	1.01 (0.93;1.09)	1.01 (0.93;1.09)	1.10 (1.02;1.18)	
ATC group J												
n	2030	1977	2123	2265	2311	2409	2520	2576	2592	2055	2902	P < 0.001
P	25.5	24.4	26.6	29.2	28.8	30.8	32.5	33.0	34.0	34.7	36.3	
PR (95% CI)	I	0.95 (0.90;1.01)	1.04 (0.99;1.10)	1.15 (1.09;1.21)	1.13 (1.07;1.19)	1.21 (1.16;1.28)	1.29 (1.22;1.35)	1.31 (1.25;1.38)	1.34 (1.28;1.41)	1.38 (1.31;1.45)	1.44 (1.38;1.51)	
ATC group N												
n	183	208	219	283	314	330	336	377	463	356	529	P < 0.001
P	2.3	2.6	2.7	3.6	3.8	4.2	4.3	4.7	5.9	5.9	6.5	
PR (95% CI)	I	1.11 (0.91;1.35)	1.21 (0.99;1.47)	1.62 (1.34;1.95)	1.69 (1.41;2.03)	1.87 (1.56;2.23)	1.93 (1.61;2.31)	2.18 (1.82;2.59)	2.74 (2.31;3.25)	2.67 (2.24;3.19)	2.97 (2.52;3.52)	
ATC group R												
n	752	725	765	811	799	766	795	739	826	554	794	P = 0.270
P	9.5	8.9	9.5	10.3	9.7	9.5	10.0	9.2	10.6	9.2	9.7	
PR (95% CI)	I	0.93 (0.84;1.03)	1.00 (0.91;1.10)	1.08 (0.99;1.19)	1.01 (0.92;1.11)	0.99 (0.90;1.09)	1.05 (0.95;1.15)	0.97 (0.88;1.07)	1.11 (1.01;1.22)	0.96 (0.87;1.07)	1.02 (0.93;1.12)	

Notes: Prevalences are standardized to age distribution in 1999; prevalence ratios are adjusted for age and smoking during pregnancy. ATC group A, drugs for alimentary tract and metabolism; ATC group D, dermatological drugs; ATC group G, gynecological drugs; ATC group J, anti-infective drugs for systemic use; ATC group N, neurological drugs; ATC group R, drugs for the respiratory system.

Abbreviations: ATC, Anatomical Therapeutic Chemical classification of drugs; n, number; P, prevalence; PR, prevalence ratio; CI, confidence interval.

than 25 years, 53.1% among women between 25 and 29 years, 57.5% among women aged 30–34 years, and 61.1% among women aged 35 years and older. Throughout the study period, women aged 25–29 years had a lower prevalence of drug use than women in other age groups (Figure 1). Drug use over time in each age group was tested for trend ($P < 0.001$ for linear trend in all age groups).

Table 2 shows prevalence of drug use stratified by calendar year and ATC group and PRs of drug use adjusted for age and smoking. Anti-infective drugs were the most prevalent drugs used by the primiparous mothers as measured by one or more dispensed prescriptions. The age-standardized prevalence of use of anti-infective drugs increased from 25.5% in 1999 to 36.3% in 2009, PR 1.44 (95% CI: 1.38; 1.51). Women younger than 25 years had a higher prevalence of anti-infective drug use (37.3%) compared with women in all other age groups: 28.1% of women between 25 and 29 years; 28.3% of women aged 30–34; and 27.8% of women aged 35 years and older. There were 14,469 (16.9%) women redeeming one or more prescriptions for UTI antibiotic drugs and 11,761 (13.7%) women redeeming one or more prescriptions for penicillin. The prevalence of UTI-specific drug use more than doubled (10.9% in 1999; 22.9% in 2009, PR 2.15 [95% CI: 1.99; 2.31]) and the increasing prevalence was observed in all age groups (data not shown). We also observed an increase over time in the prevalence of penicillin use (13.3% in 1999; 14.1% in 2009, PR 1.10 (95% CI: 1.02; 1.19)).

The age-standardized prevalence of neurological drug use increased nearly three-fold (2.3% in 1999; 6.5% in

2009, PR 2.97 [95% CI: 2.52; 3.52]) (Table 2). At any time during pregnancy, 1872 (2.2%) women used antidepressants, 582 (0.7%) used opioids, and 451 (0.5%) used anti-epileptics. Prevalence of antidepressant use increased nearly six-fold (0.8% in 1999; 4.1% in 2009, PR 5.95 [95% CI: 4.51; 7.85]).

Prevalences of gestational-period specific drug use in 1999–2000 and 2008–2009 are shown in Figure 2. Over time, prevalence of immediate pre-conception and trimester-specific use of anti-infective drugs increased. Prevalence of trimester-specific use of neurological drugs also changed over time. For example, first-trimester use increased more than three-fold from 1.4% in 1999–2000 to 4.1% in 2008–2009, PR 3.19 (95% CI: 2.73; 3.74); second trimester use increased more than four-fold from 0.8% in 1999 to 3.4% in 2009, PR 4.30 (95% CI: 3.54; 5.22); and third trimester use increased from 0.7% in 1999 to 2.3% in 2009, PR 3.54 (95% CI: 2.85; 4.40). Prevalence of immediate pre-conception use of gynecological drugs more than doubled from 1999–2000 to 2008–2009 (3.9% in 1999–2000; 9.3% in 2008–2009, PR 2.18 (95% CI: 2.00; 2.39), whereas third-trimester use almost halved from 3.2% in 1999–2000 to 1.8% in 2008–2009, PR 0.57 (95% CI: 0.49; 0.66).

Discussion

Use of prescribed reimbursed drugs increased modestly (6.5% in absolute terms) from 1999 to 2009 in this population of almost 86,000 primiparous women. From 2001 to 2005, the Danish Institute of Public Health reported a 24% increase of prescribed drug use measured in defined daily doses (DDDs) among the general Danish population.²⁴ The

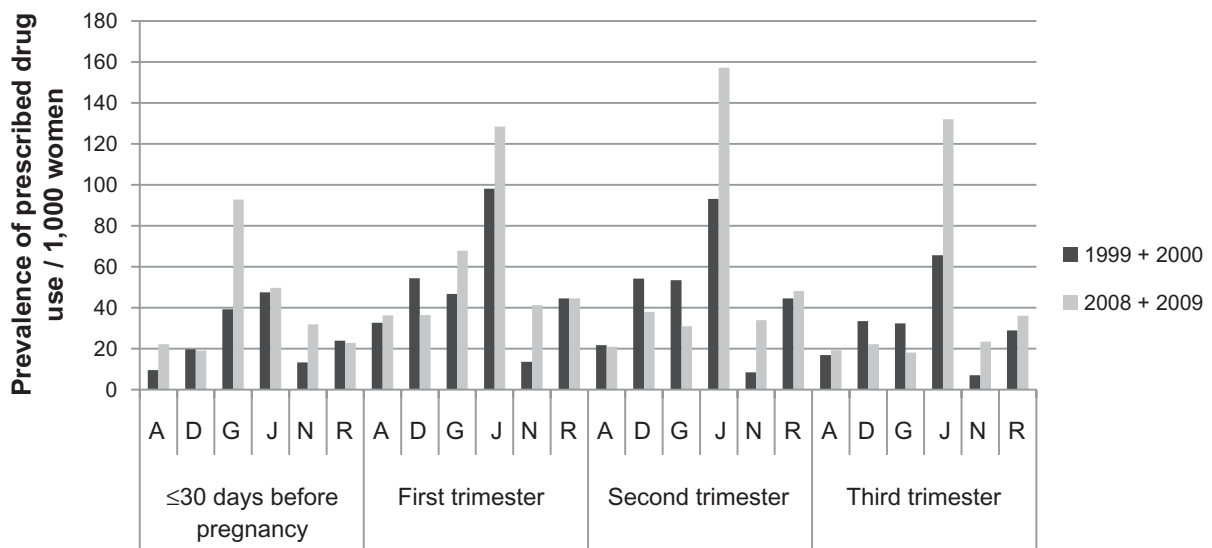


Figure 2 Prevalence (per 1000 women) of immediate pre-conception and trimester-specific drug use among primiparous women for the most commonly prescribed ATC groups: 1999–2000 and 2008–2009.

Notes: *ATC group A: drugs for alimentary tract and metabolism; ATC group D: dermatological drugs; ATC group G: gynecological drugs; ATC group J: anti-infective drugs for systemic use; ATC group N: neurological drugs; and ATC group R: drugs for the respiratory system.

observed modest increase in drug use among women giving first birth could thus be a reflection of this general population trend. The overall prevalence of drug use increased with age; however, increasing age of primiparous women did not explain the overall increase in prevalence of drug use over time. Anti-infective drugs were used with the highest prevalence as measured by one or more prescription dispensation. Prevalence of antidepressant use increased substantially over the observation period, but the absolute prevalence remained low.

Prevalence of drug use in pregnancy was on the same order of magnitude in other Nordic countries as in the present study. In Sweden (2007), the prevalence of drug use was 58% among pregnant women;⁷ in 2004–2006, in Norway, prevalence of drug use during pregnancy was 57% at any time during trimester 1–3 among first singleton pregnancies,³ while in Finland, the prevalence of use was 46% in 1999.⁵ Comparability of findings is expected as Nordic countries have similar health care and record-keeping practices.²⁵

Non-Nordic countries have reported higher prevalence of drug use during pregnancy.^{1,2,4} According to records from the French Health Insurance Service, 99% of women in Southwest France receive prescribed drugs during pregnancy.⁴ In the United States, 82% of pregnant women used prescribed drugs, based on data collected from the Health Maintenance Organizations (HMO) in 1996–2000.¹ Both in France and in the United States, the reported drug use includes certain OTC medications, such as iron, folic acid, and pregnancy vitamins. In particular, in the United States (in contrast to Denmark), pregnant women receive prescriptions for pregnancy vitamins in order to enable reimbursement, and therefore leading to a dispensation record. Thus, patterns of drug utilization during pregnancy can be expected to vary according to prescribing, reimbursement, and record-keeping practices, as well as socioeconomic differences.^{1–5}

Drug utilization patterns varied by age and by type of drug. Our finding that women aged 35 years or older had a slightly higher prevalence of overall drug use than women in younger age groups is similar to findings in a recent Irish study including 61,252 women giving birth in Dublin from 2000 to 2007.²⁶ Young age, however, has been associated with a higher use of antibiotics, as observed in a German study of about 41,000 observations based on insurance claims. This observation was confirmed in our study. The German researchers attributed higher use of antibiotics by younger pregnant women to higher rates of infections in this age group.²⁷ Screening for bacteriuria as part of routine

examination of pregnant women was introduced in Denmark in 1998,^{22,23} probably partially explaining our observation of increased use of UTI-specific drugs among women giving first birth throughout the study period. In 2001, some drugs used in treatment of gynecological infections were re-coded from gynecological drugs to the anti-infective drugs for systemic use,²⁸ which may account for some of the decrease seen for gynecological drugs and some of the increase seen for anti-infective drug use observed in our study. An increased prevalence of prescribed antidepressant drug use seen in this study was also reported in the United States.^{29,30} Exposure to antidepressants (selective serotonin reuptake inhibitors [SSRIs] in particular) in early pregnancy has been associated with an increased risk of adverse neonatal effects.^{14,31,32} That, together with our findings that use of neurological drugs increased in early pregnancy during our study period, may call for further attention.

It is important to acknowledge different strengths and weaknesses of our study when interpreting our results. Our large and well defined study population contained data from a uniform health care system with complete coverage and universal access. We used data from a system of automatic reimbursement and routine electronic record-keeping. This enabled us to avoid recall bias, and estimate drug utilization systematically.³³

We focused on trends in use of broad groups of prescription drugs according to major anatomical ATC-groups in order to give the general descriptive picture of drug utilization patterns among primiparous women. We did not aim to specifically address utilization of known or potential teratogens. Reports that almost 20% of Canadian women (study population = 18,575)³⁴ and 10% of US women (study population = 152,531)¹ used prescription drugs with potential or clear fetal risk during pregnancy call for further attention. However, the teratogenic potential of many drugs is unknown³⁵ and deserves special investigation.

The Aarhus University Prescription Database lacks information on dispensation of OTC drugs, in-hospital treatment, or sales of nonreimbursed prescribed drugs.¹⁸ Therefore the overall prevalence of prescription drug use among women giving first birth is underestimated and caution about conclusions regarding the observed change of drug utilization patterns in specific ATC-groups, eg neurological drugs, need to be considered. Furthermore, because we used information on redeemed prescriptions, we had no data about the true drug intake, potentially leading to overestimation of the actual use of the purchased drugs.³⁶ Although we examined the effect on utilization of maternal

age and self-reported smoking, we had no data on other factors, such as social status and years of education, which could also explain some of the change in use. Further, we restricted the study population to primiparous women to maximally remove the effects of age from evaluating the trends of drug use.

Authors' contributions

AB, MN, EAN, and VE have all substantially contributed to study conception, design, and interpretation of data. AB and VE drafted the article. AB and HH analyzed the data, and HH participated in dataset creation. All authors revised the paper critically and approved the final version.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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