TRENDS IN ANTI-INFECTIVE DRUGS USE DURING PREGNANCY

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ABSTRACT

Background
Development of knowledge in understanding the use of anti-infective drugs during pregnancy has been limited by difficulties in testing medications in pregnant women and lack of evidence-based data. Overuse of broad spectra agents is associated with development and spread of bacterial resistance, a problem that is faced as a significant threat to the public health.

Objectives
To describe trends in use of general and broad spectrum anti-infective drugs during pregnancy.

Methods
We used the Quebec Pregnancy Registry to analyse trends for use of oral anti-infectives dispensed during pregnancy for the five-year period comprised between January 1998 and December 2002. Trends in use were assessed for classes of anti-infectives and for broad-spectrum drugs. Descriptive statistics were used to summarize the characteristics of the study population. Annual trends for the use of anti-infective drugs were analyzed using the Cochran-Armitage test.

Results
The use of anti-infective drugs and broad spectrum agents during pregnancy decreased from 1998 to 2002 ($p \leq 0.05$ for trends). The classes that showed increasing trend for use were: macrolides, quinolones, tetracyclines, urinary anti-infective drugs and antimycotics. Use of penicillins and sulfonamides decreased. Azithromycin showed a remarkable increase in its use: 0.04% of all anti-infective prescriptions in 1998, compared to 10.16% in 2002.

Conclusions
Decrease in the use of broad-spectrum drugs may have been caused by a positive impact of data issued from evidence in everyday life clinical practice. More data is needed to evaluate the impact of the knowledge transfer from evidence-based studies on prescription's trends during pregnancy.

Key Words: *Anti-infective drugs; pregnancy; Quebec Pregnancy Registry; trends*

Physicians and health care providers face on a daily basis the question of whether or not to prescribe anti-infective drugs to pregnant women. When an infection occurs during pregnancy, it can be associated with obstetric complications, and physicians can be reluctant to prescribe anti-infectives since some of them (e.g., tetracyclines) are known to be teratogens or may have a post-natal toxic effect on the newborn (e.g., nitrofurantoin).[1,2] On the other hand, the use of anti-infective drugs in pregnancy has been cited as one of the main causes of decrease in maternal and perinatal mortality in industrialized countries.[3]

An important issue related to the use of such drugs during pregnancy is the choice of an

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effective therapeutic regimen in situations where resistant infections are life-threatening. In Canada, the Canadian Committee on Antibiotic Resistance (CCAR) encourages health care professionals to prescribe fewer anti-infective drugs in an effort to decrease resistance.[4] Use and overuse of broad spectra anti-infective drugs is associated with development and spread of bacterial resistance, a problem that is faced by health care organizations as a significant threat to the public health.[4] However, the development of knowledge in understanding the use of broad spectrum agents during pregnancy has been in stalemate in comparison to other areas of therapeutics, due mainly to difficulties in testing medications in pregnant women and lack of good evidence-based data.[5]

In this study, we describe trends in prescription of general and broad spectrum anti-infective drugs during pregnancy in the province of Quebec, Canada, over a period of five years.

METHODS

Data Sources

The study was conducted using the Quebec Pregnancy Registry, which contains data on all pregnancies with public funded drug plan coverage occurring in Quebec between January 1st 1998 and December 31st 2002. This registry was built with the linkage of three administrative databases: 1) the *Régie de l'assurance maladie du Québec* (RAMQ), 2) Med-Echo database, and 3) the *Institut de la statistique du Quebec* (ISQ). The details of the final Quebec Pregnancy Registry content can be found in previous work.[6] The use of data from the Registry was approved by the CHU Sainte-Justine's ethics committee, and the '*Commission d'Accès à l'Information du Québec*' (CAI).

Study Population

Anti-infective use was analysed for the first gestation of pregnant women meeting the following criteria: 1) being between 15 and 45 years of age at the date of entry in the registry defined as the first day of gestation and 2) continuously insured by the RAMQ drug plan for at least 12 months prior to the first day of gestation, during pregnancy, and for at least 12 months following pregnancy.

Trends in Anti-infective Drugs Use

We analysed trends for new prescriptions of oral systemic anti-infective drugs dispensed during pregnancy for the five-year period comprised between January 1st 1998 and December 31st 2002. Each year was considered separately. Trends in use were assessed for overall exposure (exposed *versus* non-exposed) and for the following American Hospital Formulary Service (AHFS) classes: antifungals (AHFS 8:12:04), cephalosporins (AHFS 8:12:06), macrolides (AHFS 8:12:12), penicillins (AHFS 8:12:16), quinolones (AHFS 8:12:18), sulfonamides (AHFS 8:12:20), tetracyclines (AHFS 8:12:24), other antibacterials (AHFS 8:12:28), antimycobacterials (AHFS 8:16), and urinary anti-infectives (AHFS 8:36). We also analysed trends for individual drugs (ampicillin, amoxicillin, azithromycin, ciprofloxacin, clarithromycin, clindamycin, doxycycline, erythromycin, fluconazole, metronidazole, nitrofurantoin, and sulfamethoxazole/trimethoprim (SXT)) and for broad spectrum anti-infectives (ampicillin, amoxicillin/clavulanate, azithromycin, cefuroxime, cephalexin, ciprofloxacin, clarithromycin, clindamycin, doxycycline, erythromycin, fluconazole, levofloxacin, metronidazole, minocyclin, moxifloxacin, ofloxacin, nitrofurantoin, and SXT).

Statistical Analysis

Descriptive statistics were used to summarize the characteristics of the study population and to compare anti-infective use during pregnancy according to calendar year. Prevalence of anti-infective drug use during pregnancy for each year was calculated by dividing the number of women filling at least one prescription for an anti-infective drug in each 12-month period by the total number of women that met eligibility criteria for that year. Prevalence of use for each class and individual molecule was calculated by dividing the total number of new prescriptions for each class/type of anti-infective by the total number of filled prescriptions for a given period. Annual trends in anti-infective prescriptions were analyzed using the Cochran-Armitage test for trend. All analyses were two-sided and $p \leq 0.05$ was considered significant. SAS version 9.1 (SAS Institute, Cary, NC) was used to conduct the analyses.

RESULTS

97,680 pregnant women within the Quebec Pregnancy Registry met eligibility criteria and were included in the study. From this total, 23,913 (24.5%) were exposed at least once to an anti-infective drug. There were 34,753 filled prescriptions for anti-infective drugs during the five year period considered: 33,510 were new filled prescriptions (3.6% were refill prescriptions).

The overall use of anti-infective drugs during pregnancy decreased from 1998 to 2002 ($p \leq 0.05$ for trends, see Table 1). The same result was found when the analysis considered the use of broad spectrum agents; for this class, the highest prevalence of use was observed in 2000: 38.9% of all anti-infectives prescribed in that year were broad spectrum agents.

The classes that showed increasing trend for use were: macrolides, quinolones, tetracyclines, urinary anti-infective drugs and antimycotics. Use of penicillins and sulfonamides decreased, while cephalosporins, anti-protozoals and antimycobacterials showed no trend.

Increased use of azithromycin, nitrofurantoin and fluconazole was observed from 1998 to 2002. Azithromycin showed a remarkable increase in its use: 0.04% of all anti-infective prescriptions in 1998, compared to 10.2% in 2002. Drugs like amoxicillin, erythromycin and SXT showed decrease in their use during the same period. These results and the effectives for each year are summarized in Table 1.

DISCUSSION

The decrease in the use of anti-infective drugs (all combined) and broad spectrum agents during pregnancy observed in our cohort may indicate that physicians are concerned about prescribing anti-infective drugs once pregnancy is diagnosed. These results may be a sign that Canadian clinicians are compliant with the recommendations of the CCAR; the use of narrow-spectrum anti-infective agents is preferred over those with a broad spectrum for the treatment of well-established infections. Studies on the use of broad spectrum anti-infective drugs in other clinical contexts showed increased trends in prescription.[7] Prevalence of use of these drugs during pregnancy in other countries varies.[8]

Several studies report an increased risk of congenital malformations after exposure to SXT.[9] Despite the fact that this drug is recommended for the treatment of urinary, respiratory, and gastrointestinal infections, the impact of these studies may have caused physicians to decrease prescription of this drug during pregnancy, as observed in our study population. This reduction is probably related to the increase in the use of nitrofurantoin, as a SXT substitute. Physicians may feel more confident prescribing nitrofurantoin for indications where this switch is justified. Nitrofurantoin is one of the most used urinary anti-infective drugs during pregnancy, mainly because of its well known safety profile and efficacy.[10] However, increasing nitrofurantoin resistance undermines this choice for empiric regimens.

The tapering in the use of SXT and penicillins may partially explain the increase in the use of ciprofloxacin, a quinolone anti-infective commonly prescribed for the treatment of urinary tract infections. Quinolones, as a class also showed increased trends in prescription. Despite the theoretical risk of foetotoxicty after exposure to quinolones, the use of ciprofloxacin has not been associated with the risk of congenital malformations.[9] We believe that, in our study, women were exposed to this drug in the first trimester of pregnancy, before being aware of their condition.[6] Exposure to a potentially harmful anti-infective drug in the first trimester of gestation may be explained by the fact that 50% of all pregnancies in North America are unplanned.[1] Furthermore, oral fluconzaole became more popular than topical azoles for treatment of vaginal candidiasis.[9] Doxycycline is commonly prescribed after a surgical abortion, and its use is related to the raise in these procedures in Quebec during the study period.[10]

Finally, we observed that macrolides showed increased trends in its use. Azithromycin was the individual drug responsible for this effect. Bacterial resistance associated with penicillins and the convenience of the short treatment course and one daily dosage regimen of azithromycin might have contributed to its popularity.

Azithromycin and erythromycin have a similar mechanism of action. However, azithromycin has advantages over erythromycin: better efficacy, broader spectra, and better tolerability. Its main

indications for use include treatment of mild to moderate infections of the respiratory tract and chlamydial cervicitis. The single oral dose administration increases compliance when compared to the standard erythromycin or amoxicillin 7-day regimen.[11] Growing evidence on the safety and efficacy of azithromycin during pregnancy may have played a role in the raise in its use found in our cohort. Once again, prescription practice seems to be related to the evidence of safety and effectiveness of medications during pregnancy. Nevertheless, there is controversy on the diagnosis of pregnancy infections in the absence of bacterial culture data; emergency physicians are usually required to choose empiric therapy without such information.[12]

This study was conducted on prospectively collected data obtained from administrative databases and hence, it has some limitations. Prevalence and trends of anti-infective drug use were calculated on the basis of the drugs dispensed to study subjects and do not reflect the actual intake. However, the provincial drug plan requires that the beneficiary pays a portion of the costs of the prescription medications. This increases the likelihood that prescriptions that are filled are in fact consumed.

In conclusion, physicians seem to be concerned in rationalizing anti-infective prescription practice during pregnancy. Decrease of broad-spectrum anti-infective drugs use may have been caused by a positive impact of data issue from evidence in everyday life clinical practice. More data are needed to evaluate the impact of the knowledge transfer from evidence-based studies on prescription's trends during pregnancy.

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TABLE 1 Trends in anti-infective drugs use

Anti-infective drugs (n, %)	Number of pregnant women by year					Total	Cochran-Armitage Test (p value)
	1998 (n=25705)	1999 (n=22617)	2000 (n=19093)	2001 (n=17338)	2002 (n=12927)		
Pregnant women taking an anti-infective drug [a]							
Yes	6436 (25.04%)	5524 (24.42%)	4794 (25.11%)	4171 (24.06%)	2988 (23.11%)	23913 (24.48%)	0.0002 - decrease
No	19269 (74.96%)	17093 (75.58%)	14299 (74.89%)	13167 (75.94%)	9939 (76.89%)	73767 (75.52%)	
						97680 (100%)	
Prescriptions filled for anti-infective drugs							
New prescriptions	9062 (97.24%)	7758 (96.52%)	6770 (96.94%)	5788 (95.09%)	4132 (95.48%)	33510 (96.43%)	
Refill prescriptions	254 (2.76%)	280 (3.48%)	214 (3.06%)	299 (4.91%)	196 (4.52%)	1243 (3.57%)	
Spectrum of Anti-infective drug used[b]							
Broad spectrum	3529 (38.94%)	2726 (35.14%)	2075 (30.65%)	1679 (29.01%)	1137 (24.52%)	11146 (33.26%)	<.0001 - decrease
Narrow spectrum	5533 (61.06%)	5032 (64.86%)	4695 (69.35%)	4109 (70.99%)	2995 (72.48%)	22364 (66.74%)	
						33510 (100%)	
Classes of anti-infective drugs used[b]							
Penicillins	4980 (54.95%)	4132 (53.26%)	3154 (46.59%)	2553 (44.11%)	1712 (41.43%)	16531 (49.33%)	<.0001 - decrease
Macrolides	1362 (15.03%)	1129 (14.55%)	1209 (17.86%)	1152 (19.90%)	814 (19.70%)	5666 (16.91%)	<.0001 - increase
Quinolones	305 (3.37%)	348 (4.49%)	359 (5.30%)	337 (5.82%)	293 (7.09%)	1642 (4.90%)	<.0001 - increase
Cephalosporins	437 (4.82%)	399 (5.14%)	348 (5.14%)	258 (4.46%)	172 (4.16%)	1614 (4.82%)	0.0579
Tetracyclines	294 (3.24%)	256 (3.30%)	288 (4.25%)	402 (6.95%)	275 (6.66%)	1515 (4.52%)	<.0001 - increase

UTI	341 (3.76%)	308 (3.97%)	312 (4.61%)	301 (5.20%)	218 (5.28%)	1480 (4.42%)	<.0001 - increase
Antimycotics	307 (3.39%)	298 (3.84%)	293 (4.33%)	244 (4.22%)	208 (5.03%)	1350 (4.03%)	<.0001 - increase
Anti-protozoals	342 (3.77%)	289 (3.73%)	273 (4.03%)	121 (2.09%)	208 (5.03%)	1233 (3.68%)	0.9878
Others	270 (2.98%)	252 (3.25%)	271 (4.00%)	239 (4.13%)	135 (3.27%)	1167 (3.48%)	0.005
Sulfonamides	383 (4.23%)	291 (3.75%)	202 (2.98%)	151 (2.61%)	77 (1.86%)	1104 (3.29%)	<.0001 - decrease
Antimycobacterials	41 (0.45%)	56 (0.72%)	61 (0.90%)	30 (0.52%)	20 (0.48%)	208 (0.62%)	0.7815
Type of anti-infective drugs used[b]							
Amoxicillin	3529 (38.94%)	2726 (35.14%)	2075 (30.65%)	1679 (29.01%)	1137 (27.52%)	11146 (33.26%)	<.0001 - decrease
Phenoxymethylpenicillin	799 (8.82%)	848 (10.93%)	626 (9.25%)	549 (9.49%)	349 (8.45%)	3171 (9.46%)	0.2756
Erythromycin	663 (7.32%)	419 (5.40%)	286 (4.22%)	178 (3.08%)	103 (2.49%)	1649 (4.92%)	<.0001 - decrease
Azithromycin	4 (0.04%)	138 (1.78%)	436 (6.44%)	558 (9.64%)	420 (10.16%)	1556 (4.64%)	<.0001 - increase
Clarithromycin	418 (4.61%)	330 (4.25%)	308 (4.55%)	267 (4.61%)	177 (4.28%)	1500 (4.48%)	0.7643
Ciprofloxacin	288 (3.18%)	272 (3.51%)	260 (3.84%)	249 (4.30%)	229 (5.54%)	1298 (3.87%)	<.0001 - increase
Nitrofurantoin	272 (3.00%)	256 (3.30%)	270 (3.99%)	265 (4.58%)	191 (4.62%)	1254 (3.74%)	<.0001 – increase
Metronidazole	340 (3.75%)	286 (3.69%)	272 (4.02%)	116 (2.00%)	207 (5.01%)	1221 (3.64%)	0.9156
Doxycycline	233 (2.57%)	164 (2.11%)	213 (3.15%)	321 (5.55%)	217 (5.25%)	1148 (3.43%)	<.0001 - increase
Fluconazole	242 (2.67%)	250 (3.22%)	249 (3.68%)	209 (3.61%)	176 (4.26%)	1126 (3.36%)	<.0001 - increase
Trimethoprime-sufamethoxazole	381 (4.20%)	290 (3.74%)	202 (2.98%)	150 (2.59%)	75 (1.82%)	1098 (3.28%)	<.0001 - decrease
Clindamycine	242 (2.67%)	229 (2.95%)	246 (3.63%)	204 (3.52%)	115 (2.78%)	1036 (3.09%)	0.0444

a Based on the number of pregnant women per year

b Based on the number of new filled prescriptions