Université de Montréal

USE OF ANTI-INFECTIVE DRUGS DURING PREGNANCY: PREVALENCE, PREDICTORS AND THE RISK OF PRETERM BIRTH AND SMALL-FOR-GESTATIONAL-AGE NEWBORNS

par

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Use of anti-infective drugs during pregnancy: prevalence, predictors of use and the risk of preterm birth and small-for-gestational-age newborns

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RÉSUMÉ

Les anti-infectieux sont parmi les médicaments les plus utilisés pendant la grossesse. Les indications pour l'utilisation de ces médicaments, telles que les infections bactériennes, figurent parmi les facteurs de risque les plus importants pour la prématurité et les enfants nés petits pour l'âge gestationnel (« Small-for-gestational-age », SGA). Ces complications de la grossesse peuvent avoir des incidences sur la santé du nouveau né et sur son développement futur. Compte tenu des impacts sur la santé de la mère et de l'enfant, la prise en charge et le traitement efficace de ces infections sont impératifs. Cependant, l'utilisation des anti-infectieux, pour éviter des issues de grossesse défavorables, fait l'objet d'une controverse dans la littérature. Cette controverse est en partie liée à la qualité méthodologique discutable des études disponibles sur le sujet.

Les quatre études présentées dans cette thèse ont donc pour objectif d'investiguer l'utilisation des anti-infectieux durant la grossesse ainsi que d'évaluer le risque de prématurité et de SGA après utilisation de ces médicaments en période gestationnelle. Une révision systématique de la littérature sur l'utilisation du métronidazole durant la grossesse est également présentée. Nous avons utilisé, comme source de données le Registre des Grossesses du Québec, une cohorte longitudinale conçue à partir du jumelage de trois bases de données administratives de la province du Québec (RAMQ, Med-Echo et ISQ). Le registre fournit des informations sur les prescriptions, les services pharmaceutiques et médicaux, ainsi que des donnés sur les soins d'hospitalisation de courte durée et démographiques. Les deux premières études présentées dans cette thèse ont eu pour objectif d'évaluer la prévalence, les tendances, les indications et les prédicteurs de l'utilisation des anti-infectieux dans une cohorte, extraite du registre, de 97

680 femmes enceintes. A l'aide d'un devis cas-témoins, les 2 dernières études ont mesuré l'association entre l'utilisation d'anti-infectieux durant les 2 derniers trimestres de grossesse et le risque de prématurité et de SGA, respectivement. Un cas de prématurité a été défini comme un accouchement survenu avant 37 semaines de gestation. Un cas de SGA a été défini comme l'accouchement d'un enfant dont le poids à la naissance se situe sous le 10ème percentile du poids normalisé à la naissance (compte tenu de l'âge gestationnel et du sexe du bébé). Les données ont été recueillies pour les agents systémiques oraux, ainsi que pour les classes et les agents individuels.

Nos résultats ont montré que la prévalence de l'utilisation des anti-infectieux durant la grossesse était comparable à celle d'autres études déjà publiées (25%). Nous avons observé une augmentation de l'utilisation des agents plus anciens et ayant des profils d'innocuité connus. Les prédicteurs de l'usage en début de grossesse identifiés sont : avoir eu plus de deux différentes prescriptions (OR ajusté = 3,83, IC 95% : 3,3-4,3), avoir eu un diagnostic d'infection urinaire (OR= 1,50, IC 95% : 1,3-1,8) et un diagnostic d'infection respiratoire (OR= 1,40, IC 95% : 1,2-1,6). L'utilisation des macrolides a été associée à une diminution du risque de prématurité (OR =0,65, IC 95% : 0,50-0,85). En revanche, les femmes ayant été exposées au métronidazole ont vu leur risque augmenté de 80% (OR=1,81, IC 95% : 1,30-2,54). L'utilisation d'azithromycine a été associée à une diminution importante du risque chez les femmes ayant un diagnostic de rupture prématurée des membranes (OR=0,31, IC 95% : 0,10-0,93). Cependant, l'utilisation de sulfaméthoxazole-triméthoprime (SXT) a été significativement associée à une augmentation du risque de SGA (OR= 1,61, IC 95% : 1,16-2,23), tandis que celle des anti-infectieux urinaires a été associée à une diminution du risque (OR= 0,80, 95%CI : 0.65-0.97).

Les conclusions de nos travaux suggèrent que l'utilisation des macrolides et des pénicillines diminuent le risque de prématurité et de SGA. Nous devons considérer l'utilisation de différents choix thérapeutiques tels que l'azithromycine, lors de la prise en charge des infections pouvant induire la prématurité et le SGA.

Mots clés : anti-infectieux, grossesse, prématurité, petit pour l'âge gestationnel, Registre des Grossesses du Québec, devis cas-témoin.

ABSTRACT

Anti-infective drugs are among the most used medications during pregnancy. Gestational infections are related to some adverse pregnancy outcomes, such as preterm birth and infants born small for their gestational age (SGA), which increases the risk of mortality and long-term morbidity. Given its health impacts, prompt management and treatment of these infections are warranted. However, there is some controversy on the use of anti-infective drugs to prevent adverse pregnancy outcomes, such as preterm birth. Furthermore, there is growing concern regarding its independent effects on these outcomes, when treatment of maternal infections is instituted.

Therefore, we conducted 4 large population-based studies aimed to investigate the gestational use of anti-infective drugs during pregnancy and the risk of preterm birth and SGA. In addition, we systematically reviewed the available evidence on the use of metronidazole during gestation. We used data from the Quebec Pregnancy Registry, a longitudinal population-based cohort established with the linkage of three administrative databases from the province of Quebec (RAMQ, Med-Echo and ISQ). Data are available on prescriptions, pharmaceutical and healthcare services, acute care hospitalization and patient demographics. For study 1 and 2, we conducted a drug utilisation review within a cohort of 97 680 pregnant women. Study 3 and 4 were two independent case-control studies. Cases of preterm birth were defined as those with a delivery occurring before the 37th week of gestation (study 3). Cases of SGA were defined as a pregnancy resulting in a baby's weigh adjusted for gestational age and gender <10th percentile, according to the Canadian gender-specific reference curves (Study 4). Oral use of anti-infective drugs during the last two trimesters of pregnancy was the exposure

definition for both studies. Independent analyses were done to assess the risk for different classes of anti-infectives and individual agents.

Our results indicate that the use of anti-infective drugs during pregnancy is prevalent (25%). Use of well-known agents increased once pregnancy was diagnosed, and the most frequent indications for use were respiratory and urinary infections. Predictors associated with use were having more that 2 different prescribers (adj. OR= 3.83, 95% CI: 3.3-4.3), having a diagnosis of urinary tract infections (adj. OR= 1.50, 95% CI: 1.3-1.8) and respiratory tract infection (adj. OR= 1.40, 95% CI: 1.2-1.6). The use of macrolides was associated with a decreased risk of preterm birth (adj. OR=0.65, 95% CI: 0.50-0.85), whereas metronidazole increased the risk (adj. OR=1.81, 95% CI: 1.30-2.54). Azithromycin had a protective effect in women with premature rupture of membranes (adj. OR=0.31, 95% CI: 0.10-0.93). Use of sulfamethoxazole/trimethoprim was associated with an increased risk of SGA (adj. OR= 1.61, 95%CI: 1.16-2.23), whereas the use of urinary anti-infectives decreased the risk (adj. OR= 0.80, 95%CI: 0.65-0.97).

The results of this thesis suggest that the use of macrolides and penicillins decrease the risk of preterm birth and SGA. Health care professionals should consider other therapeutic alternatives to metronidazole and sulfonamides, such as azithromycin.

Keywords : anti-infective drugs, pregnancy, preterm birth, small for gestational age, Quebec Pregnancy Registry, case-control study.

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LIST OF ABBREVIATIONS

AHFS	American Hospital Formulary Service
ATC	Anatomical Therapeutic Chemical
bid	Twice a day
BMI	Body-mass index
BV	Bacterial vaginosis
CCAR	Canadian Committee on Antibiotic Resistance
CI	Confidence interval
CHU	Centre hospitalier universitaire
FDA	Food and Drug Administration
g	Gram
GBS	Group B streptococcus
G6PD	Glucose-6-phosphate-dehydrogenase
ICD-9	International Classification of Diseases – 9th edition
IM	Intramuscular
ISQ	*Institut de la Statistique du Québec*
IUGR	Intrauterin growth restriction
IV	Intravenous
Med-Echo	*Maintenance et exploration des donnés pour l'étude de la clientele hospitaliere*
mg	Milligram
OR	Odds ratio
P	P value
PID	Pelvic inflammatory isease
po	Per os
PROM	Premature rupture of membranes
qid	Four times a day
RAMQ	*Regie de l'assurance maladie du Québec*

RR	Relative risk
RCT	Randomised clinical trials
SAS	Statistical Analysis System
SD	Standard deviation
SGA	Small-for-gestational age
SMX	Trimetroprim-Sulfmethoxazole
STI	Sexually transmitted infection
tid	Three times a day
USA	United States of America
UTI	Urinary tract infection

DEDICATION

To my father, Evaldo Toscano-Santos for his unconditional support of my education.

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Chapter 1
INTRODUCTION

Anti-infective drugs are among the most frequently used medications during pregnancy [1]. It is estimated that 17 to 41% of pregnant women are exposed to these drugs at least once during gestation [2-4].

Given that 50% of the fetus genetic material is derived from the father, the fetus's susceptibility to rejection by the maternal immune system is similar to the susceptibility of a transplanted organ. Evidence indicates that the maternal immune system may tolerate fetal antigens by suppressing cell-mediated immunity while retaining normal humoral immunity. These changes occur at the maternal-fetal interface but may also affect systemic immune responses to infection. In fact, these immunologic adaptations of pregnancy may induce a state of increased susceptibility to certain intracellular pathogens, including viruses and bacteria, which increase the risk of infection [5]. Therefore, when compared to their non-pregnant counterparts, pregnant women are more susceptible to infections, being hence more prone to use antimicrobial drugs [6].

When occurring at specific periods, prevalent indications for anti-infective use during gestation are related to some adverse pregnancy outcomes. For example, urinary tract infections (UTIs) diagnosed during the last two trimesters of pregnancy, are associated with an increased risk of premature rupture of membranes (PROM), preterm birth and infants born small for their gestational age (SGA) [7, 8]. These babies are at increased risk of long-term morbidity, including neurologic and behaviour problems, delayed growth during childhood, hypertension, obesity, and type II diabetes in adulthood [9].

Furthermore, bacterial infections during pregnancy are responsible for most of ante-partum admissions to the maternal–fetal medicine units [10]. Hence, given its impacts on the health of the mother and the fetus, when an infection occurs during gestation, prompt management and antibiotic treatment is warranted [11]. Indeed, the effective treatment of gestational infections is one of the main causes of the decrease in maternal and prenatal mortality in industrialized countries [12].

Over the years, there has been growing concern regarding the independent effect of anti-infective drugs used during gestation on adverse pregnancy outcomes, when treatment of maternal infections is instituted [13, 14]. There is increasing evidence that some classes of antimicrobials commonly prescribed during pregnancy may present unsuspicious non-antibiotic properties in the modulation of important physiological process, which are essential for the fetal development and maturation, such as bone metabolism, angiogenesis and apoptosis inhibition [15, 16]. Furthermore, It has been hypothesized that the action of some anti-infective drugs can culminate in the release of a microorganism's metabolic products into the maternal genito-urinary tract [17]. This effect could trigger the inflammatory pathway leading to placenta-mediated adverse outcomes, such as preterm birth and SGA [18, 19]. This issue remains unsolved, and there is still some controversy on the use of some classes of these drugs for the treatment of gestational infections and prevention of these adverse outcomes [20]. Thus, the independent effect of anti-infective drugs on preterm birth and SGA requires further investigation.

This thesis presents 5 studies conceived to furnish new evidence-based data on the use of anti-infective drugs during pregnancy. A drug utilization review (Study 1 and 2) that describes prevalence, trends, indications and predictors of use, is followed by the risk assessment of preterm birth (Study 3) and small-for-gestational-age newborns (Study 4) after exposure to anti-infective

drugs, according to trimester of exposure and class of anti-infective. Moreover, this thesis includes a review of the available evidence on the use of metronidazole during pregnancy (Study 5). The main results are presented in the form of articles already published in scientific journals, or in the form of manuscripts submitted for publication.

Chapter 2
LITERATURE REVIEW

An anti-infective drug is a compound or substance that kills or slows down the growth of microorganisms, such as bacteria and fungus [21]. The term is often used synonymously with the term antibiotic. However, the later term defines any substance that: 1) must be produced by a living organism and, 2) is antagonistic to the growth of other microorganisms in high dilution [22]. Therefore, this definition exclude substances that kill bacteria but are not produced by microorganisms, and also exclude important synthetic antibacterial compounds, such as sulfonamides [23]. In this manuscript, we opted to use the broader term “anti-infective drug” when referring to antimicrobial drugs used in the treatment of bacterial, fungal or parasitical infections, regardless its chemical or biosynthetic origins.

The following sections describe the available evidence on the use of anti-infective drugs during pregnancy. More specifically, this chapter covers a detailed description of the classes of anti-infective drugs available, its main indications for use during pregnancy, and its potential impacts on two pregnancy outcomes of interest: preterm birth and SGA.

2.1. ANTI-INFECTIVE DRUGS AND PREGNANCY

2.1.1. Classification of anti-infective drugs

Several methods have been proposed to classify anti-infective agents, and all are hampered by exceptions and overlaps. One of the most common

classifications is based on the drug's chemical structure, mechanism of action, and indication for use [24-29]:

2.1.1.1. Beta-Lactam antibiotics and Other Inhibitors of the microorganism cell wall synthesis

These include the beta-lactam drugs (penicillins and cephalosporins), and miscellaneous agents with different chemical structures. Penicillins can be sub-grouped into narrow spectrum antibiotics (penicillins G, V and oxacillin) and wider spectrum (ampicillin, amoxicillin, piperacillin). Cephalosporins can be grouped into 1st generation agents (narrow spectrum, such as cefazolin and cephalexin) and wider spectrum agents of 2nd generation (cefotetan, cefoxitin, cefuroxime, cefaclor), 3rd generation (ceftazidime, cefoperazone, cefotaxime, ceftriaxone) and 4th generations (cefepime). Miscellaneous anti-infectives are represented by the carbapenens (imipenem, meropenem and ertapenem), aztreonam, cycloserine, vancomycin, bacitracin, and imidazole antifungal agents (miconazole, ketoconazole, and clotrimazole) [27].

During pregnancy, beta-lactam agents are active against a wide range of respiratory, gastrointestinal, cutaneous and urinary infections caused by microorganisms, such as Gram-positive cocci (*Enterococcus spp*., *Staphylococcus spp*., *Streptococcus spp*.), Gram-negative cocci (*Nesisseria* spp.), Gram-negative bacilli (*Escherichia coli*, *Haemophylus influenzae*, *Klebsiella spp*., *Proteus spp*., *Pseudomonas spp*., *Salmonela spp*.) and Spirochetes [24, 27, 30-32].

2.1.1.2. Inhibitors of the microorganism cell membrane

This class includes agents that act directly on the microorganism cell membrane, affecting permeability and leading to leakage of intracellular

compounds. Some representants of this class include the polymyxin, colistimethate, and the polyene antifungal agents, such as nystatin and amphotericin B [25].

Polymyxin has a bactericidal action against almost all gram-negative bacilli except the *Proteus* group. Nystatin and amphotericin B are effective against *Candida spp*. and *Cryptococcus spp*. [24, 27]:

These drugs are barely used during gestation [30-32].

2.1.1.3. Inhibitors of the bacterial protein synthesis

These bacteriostatic agents affect the function of the 30 S or 50 S ribosomal subunits to cause a reversible inhibition of protein synthesis. They can be grouped into broad-spectrum agents, such as chloramphenicol and tetracyclines (tetracycline, doxycycline, minocycline, tigecycline), moderate spectrum agents, such as macrolides (erythromycin, azithromycin and clarithromycin) and narrow spectrum (lincosamides, streptogramins and linezolid) [28]. The aminoglycosides irreversibly inhibit protein synthesis, being therefore, bactericidal agents. Some examples of aminoglycosides include gentamicin, neomycin, amikacin, tobramycin and kanamycin [25].

Tetracyclines are active against *Treponema pallidum*, *Chlamydia spp.*, *Mycoplasma spp*. and *Rickettsia spp*. Macrolides are used against Gram-positive bacteria, *Streptococcus pneumoniae* and *Haemophilus influenzae*. The antimicrobial spectrum of macrolides is slightly wider than that of penicillin, and, therefore, macrolides are a common substitute for patients allergic to penicillins. Beta-hemolytic *streptococci*, *pneumococci*, *staphylococci*, and *enterococci* are usually susceptible to macrolides. Unlike penicillin, macrolides have been shown to be effective against *Legionella*

pneumophila, *Mycoplasmum spp*., *Mycobacterium*, and *Chlamydia spp*. Aminoglycosides are effective against Gram-negative bacteria, such as *Escherichia coli* and *Klebsiella spp*., particularly *Pseudomonas aeruginosa* [24, 27, 28].

Tetracyclines and aminoglycosides are not recommended during pregnancy. The main risk of tetracycline use during pregnancy is a yellow-brown discolouration of teeth as a result of deposition by chelation of this agent in calcifying teeth of the infant [33]. Azithromycin is indicated for the treatment of not only upper and lower respiratory tract and cutaneous infections, but also treatment for urethritis and cervicitis caused by *Chlamydia trachomatis*. During pregnancy, spiramycin is used primarily in the treatment of protozoal infections and specifically for the treatment of toxoplasmosis. Clarithromycin is a treatment option in pregnant patients who cannot tolerate erythromycin because of adverse effects [30-32].

2.1.1.4. Antimetabolites agents

Some agents of this group specifically inhibit essential metabolic steps that are essential to microorganisms. Examples of anti-infective of this group include sulfonamides (sulfisoxazole, sulfacetamide) and the combination trimethroprim-sulfamethoxazole [34, 35]. Other agents directly affect nucleic acid metabolism, such as the fluoroquinolones of 1st generation (norfloxacin), 2nd generation (ciprofloxacin and ofloxacin), 3rd generation (levofloxacin) and 4th generation (moxifloxacin) [36].

Sulfonamides are active against Gram-positive and negative organisms, *Chlamydia spp*., and *Nocardia spp*. The combination trimethroprim-sulfamethoxazole is effective against *E.coli spp*., *Haemophylus influenzae* and *Moraxella catarrhalis*. Fluoroquinolones are effective in the treatment of

infections of the urogenital and gastrointestinal tracts caused by Gram-negative organisms, including *E. coli*, *Klebsiella spp*., *Campylobacter spp*., *Enterobacter spp*., *Pseudomonas aeruginosa*, *Salmonella spp*., and *Shigella spp*. [24].

Trimethoprim and sulphonamides are widely prescribed for the treatment of UTIs during pregnancy. However, the use should be avoided during the first trimester and late in gestation, respectively [37]. Fluoroquinolones have been associated to the development of arthropathy in immature animals and are not recommended for routine use during pregnancy [30-32].

2.1.1.5. Antimycobacterial drugs

Agents of this class are active against *Mycobacterium* spp. During pregnancy, these drugs are used against tuberculosis, leprosy and atypical mycobacterium infections [30, 31].

2.1.1.6. Miscellaneous and Urinary anti-infective agents

Metronidazole, nitrofurantoin and nalidixic acid are the most important agents of this class. Metronidazole is effective against *Bacteroides spp*., *Clostridium spp.*, *Gardenerella vaginalis*, *Helycobacter pylori*, and *Pseudomonas spp*. Nalidixic acid and Nitrofurantoin are active against many urinary tract pathogens, but not *Proteus spp.*, or *Pseudomonas spp*. [24].

Metronidazol is used for the treatment of bacterial vaginosis and trichomoniasis during pregnancy. Nitrofurantoin is used for the as a second-line treatment for asymptomatic bacteriuria and cystitis during pregnancy [30-32].

The most common infections diagnosed during pregnancy include respiratory tract infections, gastroenteritis, urinary tract infections and bacterial vaginosis [11, 38, 39]. Other less prevalent conditons include sexually transmitted infections, malaria, tuberculosis and cutaneous bacterial infections [40-42]. A more detailed description of the most important gestational infections can be found in the section 2.2.

2.1.2. Epidemiology of anti-infective drug use during pregnancy

The question of whether to prescribe anti-infective drugs to pregnant women is a dilemma faced by health care providers on a daily basis. The potential benefits need to be weighed against the risk to the fetus [31]. Physicians have been reluctant to prescribe anti-infective drugs for pregnant women because a few of them are on the list of human teratogens (e.g., tetracyclines) [30]; others have been teratogens in animal experiments (e.g., fluoroquinolones) [43]. In addition, a few may have a toxic effect postnatally (e.g., nitrofurantoin) [44].

There is discrepancy in results of the studies that investigated the use of anti-infective drugs during pregnancy. Therefore, useful comparisons between studies and interpretation of results can be challenging [45]. Prevalence of anti-infective drug use during pregnancy varies.

The use of medications by pregnant women was recorded in South Africa, and the results showed that the most commonly used medicines were analgesics, antibiotics, laxatives and antacids [46]. In Brazil, a retrospective cohort study showed that antibiotics were the third most common group of medications used during pregnancy [47]. In a Cuban study the prevalence of use was of only 4.7% [48].

A study conducted in Hungary showed that 17.2% of pregnant women were exposed to antibiotics at some point during gestation. Most women received penicillin (14.5%), while 1.2% and 0.7% of pregnant women were treated by cephalosporins and tetracyclines, respectively [3]. In Germany, 20% of pregnant women received antibiotics during gestation [2]. Higher frequency of use was observed in Denmark (28.7%) [49]. In Finland, penicillin, erythromycin and pivmecillinam were the most often used antibiotics during pregnancy comprising together 65.4% of all anti-infective prescriptions [50]. Antibiotics were the most commonly prescribed medications in a study conducted in Australia [51]. High incidence of anti-infective use in pregnancy was also observed in the United States [4, 52], where the use of nitrofurantoin, sulfonamides was considered excessive [53]. In the United Kingdom, 30% of women were exposed to at least one anti-infective drug during gestation [54].

A recent cross-sectional study conducted in a teratology information service in Canada (IMAGe center at CHU Ste-Justine in Montreal) showed that gestational exposure to anti-infectives was the third most frequently inquired class of medication by health professionals; from a total of 11 076 requests regarding medication exposure during pregnancy, 6.3% were related to anti-infective drugs [55].

2.2. INDICATIONS FOR ANTI-INFECTIVE DRUG USE DURING PREGNANCY

Anti-infective drugs are used in pregnancy for two principal purposes: curative (when an infection has already been installed) and prophylactic (to prevent infection caused by pathogenic microorganisms and its related complications for pregnancy) [56]. In practice, however there are few indications for the use of prophylactics antibiotics in pregnancy, such as group B streptococcal

infections (GBS) of the newborn and caesarean section [57, 58]. Prevalent infections during pregnancy include respiratory tract infections, UTIs and bacterial vaginosis (BV) [38]. Respiratory infections diagnosed during pregnancy are mostly of viral etiology [59-61]. In this thesis, we focus on anti-infective drugs used to treat bacterial infections. Hence, we will consider the most important conditions that require antibacterial treatment during pregnancy, such as UTIs and BV [62, 63].

2.2.1. Urinary tract infections

UTIs are one of the most common medical complications of pregnancy [11]. These infections are characterized by the presence of microorganisms in the genito-urinary tract that cannot be explained by contamination. These agents have the potential to invade the tissues of the urinary tract and adjacent structures. The infection may be limited to the growth of bacteria in the urine (which frequently doesn't produce symptoms) or it can result in several syndromes associated with an inflammatory response to remove the bacterial invasion. Actually, the term UTI represents a wide variety of conditions, including asymptomatic bacteriuria, urethritis, cystitis, acute pyelonephritis and pyelonephritis associated with bacteremia or sepsis [24].

2.2.1.1. Epidemiology of UTIs

It is estimated that 2 to 10% of pregnant women suffer from any form of UTIs [8]. These infections complicate up to 20% of pregnancies [10]. Acute cystitis is prevalent in 1 to 4% of pregnant women [64]. Despite the relatively low prevalence of pyelonephritis during pregnancy (0.5 to 2%), it is estimated that 20% to 40% of pregnant women with asymptomatic bacteriuria will develop acute pyelonephritis later in gestation [65]. Although the incidence of acute cystitis in pregnant women is similar to that in their nonpregnant counterparts,

the incidence of acute pyelonephritis in pregnant women with bacteriuria is significantly increased, compared with nonpregnant women [66]. Many studies have reported that pyelonephritis is more common during the second half of pregnancy, with an incidence peak during the last two trimesters of pregnancy [67-69]. Predictors of UTIs' asymptomatic forms include: welfare status, increasing maternal age, multiparity, unprotected vaginal intercourse, history of childhood UTIs and history of recurrent UTIs. The prevalence is also markedly increased if women present certain pre-existing medical conditions, such as diabetes mellitus, sickle cell disease, immunodeficiency states, urinary tract anatomic anomalies, spinal cord injuries and psychiatric illnesses [70].

2.2.1.2. Microbiology of UTIs

The microorganisms causing UTIs usually originate from the gastrointestinal flora of the host. The most common agent implicated in uncomplicated UTIs is *Escherichia coli*, which accounts for 85% of non-hospital setting infections [69, 71, 72]. Other microorganisms such as *Staphylococcus saprophyticus*, *Proteus spp*., *Pseudomonas aeruginosa*, *Enterococcus spp*. and *Ureaplasma urealyticum* have also been implicated [11]. Organisms causing bacteriuria are similar in both pregnant and nonpregnant women [66].

2.2.1.3. Clinical presentation of UTIs

Asymptomatic bacteriuria is characterized by bacterial colonization of the urine, with no clinical symptoms [73]. Asymptomatic bacteriuria is defined by two consecutive clean-catch urine cultures with more than 10^8 colonies of bacteria/L of urine, with a single type of bacteria [74]. It was observed that 30% of women with asymptomatic bacteriuria developed symptomatic UTI during gestation [75]. Urethritis is characterized by urethral colonization

resulting in dysuria and polyuria. Cystitis is the infection of the bladder. Common clinical manifestations are dysuria, polyuria, suprapubic discomfort, and in some cases, hematuria [37]. Pyelonephritis is an ascending UTI that has reached the pelvis of the kidney, and represents the most severe form of UTI [76]. Clinical signs and symptoms of pyelonephritis include flank pain or abdominal pain, fever, anorexia, nausea and vomiting often associated with variable degrees of dehydration, chills, headache, and tachypinea. Respiratory failure and sepsis can be present in severe forms. Fever is elevated in the acute forms [77].

2.2.1.4. UTIs and maternal outcomes

Maternal complications of UTI are a result of the tissue damage caused by bacterial endotoxins, especially in pyelonephritis [78]. The most dramatic maternal complication associated with UTIs is bacteremia and septic shock, induced by resistant pyelonephritis [11]. Other maternal complications that have been associated with UTIs during pregnancy are hypertension and preeclampsia [79, 80], anemia [81], chorioamnionitis and endometritis [76, 82].

2.2.1.5. UTIs and pregnancy outcomes

The association between perinatal outcomes and UTIs has been studied for many years [11, 63]. From a global health perspective, UTI is one of the most important and potentially preventable causes of preterm birth [83]. Intrauterine infections are thought to be responsible for up to 50% of extreme preterm births of less than 28 weeks of gestation, where both neonatal mortality and morbidity are high [83]. Among other recognized perinatal complications of UTIs, we highlight low birth weight infants, premature rupture of membranes, intrauterine growth restriction, cerebral palsy/mental

retardation and perinatal death [19, 63, 84]. There has also been a hypothesis suggesting that UTI during pregnancy is associated with child developmental delay and mental retardation [85].

2.2.1.6. Treatment of UTIs during pregnancy

Once the clinical diagnosis of UTI is established, treatment is mandatory even without confirmation of the etiological agent by culture. As a consequence, the initial antibiotic therapy has the drawback of being empirical, and a variety of different antimicrobial agents can be used for treatment [86]. It is important to remember that therapy must be safe for both mother and fetus. Table 1 summarizes most common therapeutic regimens currently proposed for the treatment of UTIs during pregnancy, according to the type of UTIs [11, 63, 77, 87-90].

Table 1. Most common therapeutic regimens currently proposed for the treatment of UTIs during pregnancy (Abbreviations: po: by mouth; q: every; bid: twice a day; tid: three times a day; qid: four times a day; SXT: Trimethoprim/Sulfamethoxazole; IM: intramuscularly; IV: intravenously).

Urinary tract infection	Treatment regimen	Treatment options	Comments
Asymp-tomatic bacteriuria	Current standard of practice is to treat pregnant patients who have asymptomatic bacteriuria with at least 3 to 7 days of an oral anti-infective agent [34, 86, 91-93].	Cephalexin 250-500 mg, po, qid. Nitrofurantoin 100 mg, po, qid or Nitrofurantoin (monohydrate/macro-crystals) 100 mg, po, bid, 7 days. Amoxicillin 500 mg, po, tid. Norfloxacin 400 mg, po, bid. Cefuroxime 250 mg, po, tid. SXT (320/1600 mg) po, once a day (avoid use during first trimester).	Single-dose regimens have been used, but showed lack of efficacy. Some authors do not recommend during gestation. SXT was associated with a theoretical increased risk of neural tube defects and it may lead to neonatal kernicterus. Nitrofurantoin was associated with theoretical risk of fetal hemolytic anemia.

Continuation of Table 1

Urethritis and cystitis	Given that the pathogens associated with urethritis and cystitis are the same as those causing asymptomatic bacteriuria, the treatment of cystitis in pregnancy is the same as the treatment for asymptomatic bacteriuria, longer courses of therapy are usually recommended (7-10 days) [86].	Cefuroxim 250 mg, po, tid. Nitrofurantoin 100 mg, po, qid or Nitrofurantoin (monohydrate/macro-crystals) 100 mg, po, bid. Amoxicillin 500 mg, po, tid. SXT (320/1600 mg) po, once a day (avoid use during first trimester).	These agents are FDA class B category [11].

Continuation of Table 1

Pyelo-nephritis	Initial treatment must be parenteral [94]. First-line therapy often includes a first-generation cephalosporin. In an inpatient setting, parenteral antimicrobial therapy usually is continued until the patient is afebrile for 48 hours [95]. The patient is switched to oral antimicrobial therapy for 2 weeks (total).	Ampicillin 2 grams, IV, q6h (+) Gentamicin 1.5-1.7/mg/kg, IV, q6 h. Gentamicin 1.5-1.7/mg/kg, IV, q8h Ampicillin-sulbactam 3 grams, IV, q6 h. Ceftriaxone 1 gram, IV/IM, q24 h. Cefuroxime 0.75–1.5 grams, IV, q8 h. Cefazolin 2 grams, IV, q6–8 h. Mezlocillin 3 grams, IV, q6 h. Piperacillin 4 grams IV q8 h. Ticarcillin/clavulanate 3.1 grams, IV, q6h.	Ampicillin monotherapy showed high incidence of resistant bacteria, and therefore, usually is used in conjunction with gentamicin. To avoid exacerbation of the renal insufficiency that commonly accompanies pyelonephritis, drug serum levels should be monitored when using aminoglycosides, such as gentamicin [95].

2.2.2. Bacterial vaginosis

2.2.2.1. Definition and microbiology

Bacterial vaginosis (BV) is a polymicrobial, superficial vaginal infection in which the normal vaginal lactobacilli flora is replaced by anaerobic bacteria and mycoplasmas, including *Gardenerella vaginalis*, *Fusobacterium* spp., *Prevotella spp*., *Pepostreptococcus spp*., *Porphyromonas spp*., *Bacteroides spp*., *Mobiluncus spp*. and *Mycoplasma hominis* [96]. Although most of these organisms are present in small numbers in the normal vagina, *Mobiluncus* is rarely found and is a sensitive marker for the diagnosis of BV [96]. On the other hand, the presence of *Gardnerella* has been reported in up to 50% of women with no signs or symptoms of BV; therefore, the finding of this agent is not diagnostic for BV [96]. In fact, it seems that the decrease in the population of *Lactobacillus spp*. as opposed to the increase in other organisms, influences the vaginal flora and may be the most important predictor for subsequent BV development [62, 97].

2.2.2.2. Epidemiology of BV

BV is a prevalent condition and the first cause of vaginitis during gestation [98]. Although the infection is present in almost 20% of pregnant women, it is difficult to know the exact prevalence of this condition, because many cases are asymptomatic or naturally occur at regular times during the menstrual cycle [96]. Most of the epidemiologic studies conducted to determine risk factors for BV, have concentrated on symptomatic cases and included results from women seeking care in STIs clinics or obstetric offices [62]. The current predictors of BV have been limited to race, sexual activity, socioeconomic status, and perhaps vaginal douching. African-American pregnant women showed 2.5-fold increased risk of BV when compared with white pregnant

women [99]. Women with lower socioeconomic status and women self reporting higher levels of psychosocial stress also have increased rates of BV [97]. Studies have found that early sexual activity, high number of lifetime sexual partners, and a prior sexually transmitted disease also increase the risk of BV [96]. Although sexually transmitted diseases and BV commonly coexist, BV is not considered a sexually transmitted disease [39]. It has been hypothesized that some behaviors, such as vaginal douching, could be potential risk factors for BV [100].

2.2.2.3. Clinical presentation of BV

The metabolism of invasive microorganism in BV increases the production of volatiles aromatic amines (such as putrescin and cadaverin) resulting in the characteristic fishy odor discharge presented by the patients [39]. The infection is clinically characterized by the presence of three of the five following Amsel criteria [101]: release of the amine fishy odour, release of amine odour after addition of potassium hydroxide, vaginal pH greater than 4.5, clue cells in the vaginal fluid and milky homogenous vaginal discharge.

2.2.2.4. BV and pregnancy outcomes

Previously considered a benign infection, BV has been related to many gynecologic conditions and complications of pregnancy including pelvic inflammatory disease (PID), post-hysterectomy vaginal cuff cellulitis, endometritis, amniotic fluid infection, preterm delivery, preterm labor, premature rupture of the membranes, and, possibly, spontaneous abortion [96, 102]. The presence of BV at a particular gestational age may be an indicator for subsequent development of pregnancy adverse outcomes. The risk may change based on BV positivity during different stages of gestation; the risk of preterm delivery due to BV in the first trimester, may be different

compared to the risk of preterm delivery in the second and third trimesters, when there is profuse placental functioning [96, 102].

The biological pathway linking BV and adverse pregnancy outcomes has been extensively studied but it has not been completely elucidated [103]. It is admitted that vaginal flora in BV is able to produce endotoxins that rends some women more susceptible to initiate the cytokines and prostaglandins cascade that culminate in preterm labour [104]. Microorganisms causing BV may ascend and infect cervix, placenta, aminiotic fluid and produce proteolitic enzymes that may culminate in premature rupture of membranes [105]. It was already demonstrated that bacterial production of phospholipases, mucinases and sialidases is more proeminent in women with BV. Those enzymes could interfere with normal physiology of tissues, increasing the chance of PID installation, premature rupture of membranes, preterm labour, chorioamniotitis and other complications [106].

2.2.2.5. Treatment of BV during pregnancy

Although BV is associated with adverse pregnancy outcomes, the only established benefit of therapy for BV in pregnant women is the reduction of signs and symptoms of vaginal infection [32]. Available evidence does not suggest any benefit in screening and treating asymptomatic pregnant women if the aim of therapy is to prevent preterm birth [107]. Therefore, treatment is only recommended for women with symptoms [108]. Because recurrence of BV is common, pregnant women should be advised to return for evaluation if symptoms recur. Therapeutic regimens include use of oral metronidazole or clindamycin [32].

Topical intra-vaginal treatment with clindamycin is not recommended, given that the use of this drug is associated with an increased risk of low birth

weight and neonatal infections [32, 102, 109-111]. Metronidazole is an anti-infective drug used against anaerobic organisms. This agent is able to cross the placenta throughout gestation, and data from animal studies suggests teratogenic properties for this drug [112]. However, there is no evidence that using metronidazole during pregnancy increases the rate of major birth defects or that there are any detectable adverse effects on fetuses [113]. Some studies suggest that the use of metronidazole during the last two trimesters of pregnancy may result in a qualitative imbalance of the normal vaginal flora [114, 115]. One of its consequences is the growth of harmful microorganisms, leading to ascending infection, stimulation of the local inflammatory process and early delivery. Therefore, the use of metronidazole during pregnancy has been controversial [113].

Table 2 summarizes most common therapeutic regimens currently proposed for the treatment of BV during pregnancy [32].

Table 2. Most common therapeutic regimens currently proposed for the treatment of BV during pregnancy (Abbreviations: po: by mouth; q: every; bid: twice a day; tid: three times a day; qid: four times a day; SXT: Trimethoprim/Sulfamethoxazole; IM: intramuscularly; IV: intravenously).

Bacterial vaginosis	Treatment regimen	Treatment options	Comments
Metronidazole	Current standard of practice is to treat pregnant patients who are symptomatic for BV with oral metronidazole.	500 mg po bid for 7 days. Metronidazole 250 mg po tid for 7 days.	Topical treatments are not recommended. Multiple studies and meta-analyses have not demonstrated an association between metronidazole use during pregnancy and birth defects.
Clindamycin		300 mg po tid for 7 days.	Topical use is not recommended.

2.3. RISKS OF ANTI-INFECTIVE DRUGS USE DURING PREGNANCY

The rational use of anti-infective drugs during pregnancy is associated with an improvement of quality of live and decrease in the rates of maternal and fetal mortality [12]. However, as with the use of other medications, the potential benefits of use need to be weighed against the risk for the fetus [31]. Furthermore, a direct independent effect of the drug itself on pregnancy outcomes cannot be excluded.

Some suggestions on the use of anti-infective drugs during pregnancy include [31]:

- Use of anti-infectives only if absolutely indicated. This includes treatment of confirmed infection, prevention of ascending infection, and prevention of early-onset neonatal sepsis;
- If possible, avoid the initiation of therapy during the first trimester of gestation;
- Selection of a safe medication, which often means an older drug with a proven track record of safety in pregnancy;
- Single-agent therapy is preferred over polypharmacy;
- Narrow-spectrum agents are preferred over those with a broad spectrum for the treatment of established infection;
- Use of the lowest effective dose.

Most of the available evidence on the use of anti-infective drugs during pregnancy was devoted to their potential teratogenic properties [33]. Teratogenesis is defined as the structural or functional dysgenesis of fetal organs. The typical manifestations of teratogenesis are restricted growth or death of the fetus, carcinogenesis, and congenital malformations, which are defined as defects in organ structure or function. These malformations may

vary in severity, with the most severe being life threatening or requiring major surgery [116].

A wide range of anti-infective agents is now available and teratogenic effects have been proved for relatively few [33]. However, only some classes of compounds have shown to be completely safe in regards to other pregnancy outcomes [31]. In addition, most clinicians felt that current resources and information about these medications are not adequate, and that their training on this topic at the undergraduate and postgraduate level is insufficient [117].

The following sections summarize the available evidence on the risk of there relevant adverse outcomes after gestational exposure to anti-infectives: congenital malformations, preterm birth and small for gestational age newborns.

2.3.1. Anti-infective drugs and the risk of congenital malformations

Several observational studies have been conducted to evaluate the association between anti-infective drugs during pregnancy and the risk of congenital malformations. Considering the low prevalence of this adverse outcome in the general population (1 to 3%) [118, 119], the majority of these studies had small sample sizes, and hence, lack statistical power to assess risk of specific malformations groups (see Table 3 for sample size information).

Penicillins and other beta-lactams have not shown to be teratogenic in humans [56]. Jepsen et al. [120] analyzed pregnancy outcomes after exposure to amoxicillin in a cohort of pregnant women obtained from population-based registries in Denmark. The authors did not find any increased risk of congenital malformations associated with amoxicillin

exposure during pregnancy (OR= 1.16, 95% CI: 0.54-2.50). Czeizel et al. [121] found similar results in a case-control study that investigated the risk of congenital abnormalities after exposure to cephalosporins (OR= 1.3, 95%CI: 0.9-1.8). No significant increase in the risk was found in another cohort of women exposed to cefuroxime during the first trimester [122] (RR=1.56, 95%CI: 0.27-9.15). Furthermore, the same team conducted a similar study with women exposed to amoxycillin/clavulanic acid, and again, no evidence of birth defects was detected (RR= 0.62, 95%CI: 0.15-2.55) [123].

Evidence of safety is also available for macrolides. A prospective multicentre study on the use of clarithromycin during pregnancy, conducted by Einarson et al. [124], compared women exposed to this agent during the first trimester of pregnancy to women exposed to other antibiotics. There were no significant differences between the two groups in the rates of major and minor malformations; 2.3 versus 1.4% for major (p= 0.86) and 5.4 versus 4.9% for minor (p = 0.96). Czeizel et al. [125, 126] evaluated the human teratogenic potential of oral use of erythromycin, spiramycin, roxithromycin, oleandomycin and josamycin treatment during pregnancy in a population-based dataset of the Hungarian Case-Control Surveillance of Congenital Abnormalities. Data were available for 38 151 subjects and no evidence of increased risk was found (OR= 1.1, 95% CI: 0.9-1.4). Congenital malformations after exposure to azithromycin was also evaluated in a more recent cohort study [127]. The results showed no statistically significant rates of major malformations, suggesting that gestational exposure to azithromycin is not associated with an increase rate of birth defects (p value= 0.89). Exposure to azithromycin, clarithromycin and roxithromycin during the first trimester of pregnancy was not associated with an increased risk of birth defects in another cohort study conducted in Israel by Bar-Oz et al. [128]. Exposure to roxithromycin alone had been previous evaluated in a smaller cohort study conducted by Chun et al. and no evidence of risk was detected. The authors did not observe any

major malformation in the exposed group whereas three cases were detected (1.8%) in the non-exposed group [129].

Given the potential impacts of UTIs during pregnancy, the safety of anti-infective drugs used to treat this condition was extensively studied. One of the first prospective cohort studies lead by Nesbitt et al. [130] did not show evidence of birth defects after exposure to nitrofurantoin (RR= 1.36, 95% CI: 0.037-70). Heiley et al. [131] analyzed data issued from medical records, and also found no significant evidence of risk after exposure (RR= 1.98, 95% CI: 0.11-35.1). Same conclusion was obtained in a meta-analysis of observational studies that assessed the risk of birth defects after exposure to nitrofurantoin during the first trimester of gestation (OR= 1.29, 95%CI: 0.25-6.57) [132]. More recent evidence corroborates previous data, and current consensus is that nitrofurantoin is safe in what concerns congenital malformations [133]. However, these studies lack statistical power to detect no association. Furtheremore, this agent can induce hemolytic anemia in the fetus or newborn, particularly in those with glucose-6-phosphate dehydrogenase deficiency [134].

Trimethoprim-sulfamethoxazole (TMP-SMX) is another medication widely used to treat UTIs. Sulfonamides as a group do not appear to pose a serious teratogenic threat; a study conducted by Ratanajamit et al. found no evidence of birth defects after exposure to sulfamethizole (OR= 1.17, 95% CI: 0.95-1.43) [135]. The same study, however, indicate a non-significant increased risk of miscarriage after exposure to this agent (OR=1.66, 95% CI: 0.92-2.99). Trimethoprim is a folic acid antagonist and its use during the first trimester has been associated with structural defects, such as neural tube and cardiovascular defects [35]. Furtheremore, there is an increased risk of kernicterus in the fetus if TMP-SMX is administered during the last six weeks of pregnancy [35].

Quinolones and fluoroquinolones are also commonly used for the treatment of UTIs. The association between fluoroquinolones and arthropathy, although observed in animals models and rarely reported in humans, has resulted in the restricted use of these drugs during pregnancy [33]. As a consequence, the safety of these drugs has been explored in a number of studies. Berkovitch et al. investigated the effect of gestational exposure to norfloxacin and ciprofloxacin on the musculoskeletal development of the fetus and found no increased risk of malformations or musculoskeletal defects [36]. Data from a prospective follow-up study conducted on the European Network of Teratology Information Services, showed no specific patterns of congenital abnormalities after exposure to quinolones [136]. A comparison of ciprofloxacin, norfloxacin, and ofloxacin, was examined by a observational cohort study conducted by Wilton et al. furnishing the same conclusion [137].

A multicenter prospective controlled study concluded that the use of fluoroquinolones during embryogenesis is not associated with an increased risk of major malformations (RR= 0.85; 95% CI: 0.21-3.49). There were no clinically significant musculoskeletal dysfunctions in children exposed to fluoroquinolones in utero [138]. Larsen et al. using administrative data, found no significant risk of congenital anormalities, after exposure to such drugs (RR= 1.30, 95% CI: 0.30-5.30) [139]. A large case-control study conducted by Czeizel et al. using data from the Hungarian Case-Control Surveillance of Congenital Abnormalities found a higher prevalence of pyloric stenosis in seven infants born from mothers who received nalidixic acid treatment during the last months of pregnancy (OR= 11.0, 95% CI: 1.3-91.4) [140]. The authors however, did not assess use during the first trimester of gestation. Therefore, most of the available evidence seems to indicate absence of teratogen properties for these drugs. Nevertheless, because of the relatively higher cost of these agents and the concern about the bacterial resistence

with frequent use, fluoroquinolones should not routinely be employed as first-line agents in uncomplicated UTIs [8].

Aminoglycoisdes antibiotics (streptomycin, gentamicin, neomycin, amikacin, tobramycin, kanamycin) have been classically associated to congenital nerve deafness in animal models. Both vestibular and auditory irreversible dysfunction can follow administration of these agents [141]. Some case series and case reports associated deafness in children born to women who received streptomycin during pregnancy [142, 143]. However, most of the evidence issued from observational data in humans did not show a clear increase in the risk [33, 144]. The most recent evidence on the subject was lead by De Hoog et al. [145], that did not find any association between exposure to tobramycin and vancomycin during pregnancy and the risk of hearing loss in neonates.

Tetracyclines are able to cross the placenta and to cause straining of the deciduous teeth [146]. Consequently, the risk is apparent only after 4 to 5 months gestation when the deciduous teeth begin to calcify. It appears that the risk of staining teeth is lower for doxycycline [147]. A statistical association was found for minor malformations after exposure to tetracycline in the first trimester of gestation [148]. A report from the Hungarian surveillance group identified 56 malformed infants whose mothers had used doxycycline during pregnancy [149]. A case–control study using this population showed a significantly increased risk when total malformations combined were considered (OR= 1.6, 95% CI: 1.1-2.3). However, when each group of malformation was evaluated separetelly, no risk was detected [149]. A more recent case–control study from the same group examining the possible teratological effect of oxytetracycline found an increased risk of a combination of neural tube defects and cardiovascular malformations (OR= 12.9; 95% CI 3.8-44.3) [150].

The same Hungarian surveillance group evaluated safety of chloramphenicol and metronidazole [151, 152]. These case-control analyses did not show any human teratogenic potential of the use of these drugs during the first trimester of pregnancy in the different groups of congenital abnormalities. Exposure to metronidazole was also evaluated with data from the Israeli Teratogen Information Service and no evidence of increased risk of birth defects was found [153]. Previous evidence from cohort studies also failed to demonstrate evidence of risk after exposure to this drug (RR= 1.2, 95% CI: 0.9-1.6) [154].

Two recent studies analyzed the risk of major congenital malformation for several types of anti-infective drugs at the same time. A retrospective cohort study using data from the Tennessee Medicaid program conducted by Cooper et al. [155] identified children with fetal exposures to ciprofloxacin, azithromycin, doxycycline, amoxicillin and compared their outcomes to children exposed to erythromycin during gestation and with infants with no fetal exposure to any antibiotics. Overall, 2.9% of children in the cohort had a confirmed major congenital malformation (range 2.5% to 3.0%). No increased risk was present in multivariable analyses for any malformations and for malformations of specific organs. In addition, Crider et al. conducted a case-control study of women who had pregnancies affected by major birth defects [156]. In adjusted models, sulfonamides were associated with anencephaly (OR= 3.4, 95% CI: 1.3-8.8), hypoplastic left heart syndrome (OR= 3.2, 95% CI: 1.3-7.6), coarctation of the aorta (OR= 2.7, 95% CI: 1.3-5.6), choanal atresia (OR= 8.0, 95% CI: 2.7-23.5), transverse limb deficiency (OR= 2.5, 95% CI: 1.0-5.9), and diaphragmatic hernia (OR= 2.4, 95% CI: 1.1-5.4). In the same study, nitrofurantoin was associated with anophthalmia or microphthalmos (OR= 3.7, 95% CI: 1.1-12.2), hypoplastic left heart syndrome (OR= 4.2, 95% CI: 1.9-9.1), atrial septal defects (OR= 1.9, 95% CI: 1.1-3.4), and cleft lip with cleft palate (OR= 2.1, 95% CI: 1.2-3.9).

Fluconazole was not associated with an increase in the risk of birth defects in a cohort study conducted by Mastroiacovo et al. (RR= 1.07, 95%CI: 0.41-2.77) [157]. Low statistical power and residual confounding was probable responsible for their results, and current consensus is that this drug should be used as a last alternative when no other choices are available.

The teratogenic risk of 11 broad-spectrum antibiotics commonly used during pregnancy and lactation was summarized in a meta-analysis of one hundred twenty-four references [20]. The authors ranged the teratogenic potential for humans from "none" (penicillin G and VK) to "unlikely" (amoxicillin, chloramphenicol, ciprofloxacin, doxycycline, levofloxacin, and rifampin) to "undetermined" (clindamycin, gentamicin, and vancomycin). Assessments of risk were based on "good data" (penicillin G and VK), "fair data" (amoxicillin, chloramphenicol, ciprofloxacin, doxycycline, levofloxacin, and rifampin), "limited data" (clindamycin and gentamicin), and "very limited data" (vancomycin).

A summary of these studies is presented in Table 3.

Table 3. Summary of the studies on the association between the use of anti-infective drugs during pregnancy and the risk of birth defects.

Authors, year and country	Study design	Class or type of anti-infective drug	Number of exposed subjects (prevalence of outcome)	Exposure window	Outcome of interested	Measure of effect (RR, OR or p values)
Aminoglycosides						
Leroux, 1950, France [142]	Case series – Prospective cohort	Streptomycin	01 (100%)	Last month of gestation	Congenital nerve deafness	*
Robinson and Combon, 1964, USA [143]	Case series - Prospective cohort	Streptomycin	02 (100%)	First trimester of gestation	Congenital nerve deafness	*
Conway and Birt, 1965, USA [144]	Case series - Prospective cohort	Streptomycin	24 (25%)	All gestation	Congenital malformations	*

Beta-Lactams						
Czeizel et al., 2001, Hungary [121]	Case-control study – Adminis-trative database	Cephalos-porins	51 (5%)	Second and third months of gestation	Major and minor congenital malformations	OR= 1.3 (0.9-1.8)
Jepsen et al., 2003, Denmark [120]	Case-control study - Adminis-trative database	Amoxicillin	401 (3%)	First trimester of gestation	Major congenital malformations	RR= 1.16 (0.54- 2.50)
Berkovitch et al., 2004, Israel [122]	Prospective cohort study	Amoxycillin/ clavulanic acid	191 (3%)	First trimester of gestation	Major congenital malformations	RR= 0.62 (0.15-2.55)
Macrolides						
Einarson et al., 1998, Canada [124]	Prospective cohort study	Clarithromycin	127 (3%)	First trimester of gestation	Major and minor congenital malformations	P= 0.86

Czeizel et al., 1999, Hungary [126]	Case-control study - Adminis-trative database	Erythromycin	113 (4%)	Second and third months of gestation	Major and minor congenital malformations	OR= 0.8 (0.5-1.4)
Czeizel et al., 2000, Hungary [125]	Case-control study - Adminis-trative database	Spiramycin, roxithromycin, oleandomycin and josamycin	31 (4.5%)	Second and third months of gestation	Major and minor congenital malformations	OR= 1.1 (0.9-1.4)
Chun et al., 2006, South-Koreal [129]	Prospective cohort study	Roxithromycin	20 (0%)	First trimester of gestation	Major congenital malformations	Not available
Sarkar et al., 2006, Canada [127]	Prospective cohort study	Azithromycin	123 (4%)	First trimester of gestation	Major congenital malformations	p= 0.42
Baz-Oz et al., 2008, Israel [128]	Case-control study - Adminis-trative database	Macrolides	161 (4%)	First trimester of gestation	Major congenital malformations	OR= 1.41 (0.47-4.23)

Quinolones

Berkovitch et al., 1994, Canada [36]	Retrospective cohort study - Adminis-trative database	Norfloxacin and ciprofloxacin	38 (3%)	First trimester of gestation	Congenital malformations of the muskulo-skeletical system	P= 0.5
Schaefer et al., 1996, Germany [136]	Prospective follow-up study	Quinolones	549 (4.8%)	First trimester of gestation	Major and minor congenital malformations	Not available
Loebstein et al., 1998, Canada [138]	Prospective cohort study	Quinolones	200 (3.5%)	First trimester of gestation	Congenital malformations of the muskuloskeleti cal system	RR= 0.85 (0.21-3.49)
Larsen et al., 2001, Netherlands [139]	Retrospective cohort study	Fluoro-quinolones	57 (3.8%)	First trimester of gestation	Major congenital malformations	RR= 1.30 (0.30-5.30)

Tetracyclines						
Czeizel and Rockenbauer, 1997, Hungary [149]	Case-control study - Adminis-trative database	Doxycycline	56 (4%)	All gestation	Major and minor congenital malformations	OR= 1.6 (1.1-2.3)
Czeizel and Rockenbauer, 2000, Hungary [150]	Case-control study - Adminis-trative database	Oxy-tetracycline	216 (4.5%)	Second and third months of gestation	Neural-tube defects	OR= 9.7 (2.0-47.1)
Urinary anti-infectives						
Nesbit and Young, 1957 [130]	Retrospective cohort study	Nitrofurantoin	30 (4%)	First trimester of gestation	Congenital malformations	RR= 1.36 (0.03-70)
Hailey et al., 1983, USA [131]	Retrospective cohort study	Nitrofurantoin macrocrystals	29 (5%)	First trimester of gestation	Congenital malformations	RR= 1.98 (0.11-35.1)

Ben David et al., 1995, Canada [132]	Meta-analysis	Nitrofurantoin	157 (4%)	First trimester of gestation	Major and minor congenital malformations	OR= 1.29 (0.25-6.57)
Czeizel et al., 2001, Hungary [133]	Case-control study	Nitrofurantoin	1079 (4.5%)	Second and third months of gestation	Major and minor congenital malformations	OR= 1.3 (1.0-1.7)
Czeizel et al., 2001, Hungary [140]	Case-control study - Adminis-trative database	Nalidixic acid	242 (4%)	Third trimester of gestation	Pyloric stenosis	OR= 11.0 (1.3-91.4)
Ratanajamit et al., 2003, Denmark [135]	Case-control study - Adminis-trative database	Sulfamethizole	3484 (3.5%)	30 days before conception	Major congenital malformations	OR= 1.17 (0.95-1.43
Crider et al., 2009, USA [156]	Case-control study - Adminis-trative database	Sulfonamides and nitrofurantoin	13155	Third month of gestation	30 selected malformations	Several measures of effect

Metronidazole

Piper et al., 1993, USA [154]	Retrospective cohort study	Metronidazole	1387 (3.8%)	First trimester of gestation	Congenital malformations	RR= 1.2 (0.9-1.6)
Czeizel and Rockenbauer, 1998, Hungary [151]	Case-control study - Adminis-trative database	Metronidazole	1706 (4.5%)	First trimester of gestation	Major and minor congenital malformations	OR= 1.14 (0.89-1.46)
Diav-Citrin et al., 2001, Israel [153]	Prospective cohort study	Metronidazole	205 (3.7%)	First trimester of gestation	Major congenital malformations	RR= 1.13 (0.30–4.23)

Others

Mastroiacovo et al., 1995, Italy [157]	Prospective cohort study	Fluconazole	226 (2.8%)	First trimester of gestation	Any congenital malformation	RR= 1.07 (0.41-2.77)
Wilton et al., 1996, UK [137]	Prescription-event monitoring	Quinolones, azithromycin and cefixime	307 (4%)	Not available	Major and minor congenital malformations	*

Czeizel et al., 2000, Hungary [152]	Case-control study - Adminis-trative database	Chloram-phenicol	52 (4.0%)	Second and third months of gestation	Major and minor congenital malformations	OR= 3.1 (1.2-7.7)
Cooper et al., 2009, USA [155]	Retrospective cohort study - Adminis-trative database	Ciprofloxacin, azithromycin, doxycycline and amoxicillin	2128 (4.5%)	First trimester of gestation	Major congenital malformations	RR= 1.29 (0.96-1.73)

2.3.2. Use of anti-infective drugs and the risk of preterm birth

2.3.2.1. Definition of preterm birth

Preterm birth is defined as childbirth occurring at less than 37 completed weeks or 259 days of gestation [158]. Preterm births can be subdivided according to gestational age: about 5% of preterm births occur at less than 28 weeks' (extreme prematurity), about 15% at 28–31 weeks' (severe pre maturity), about 20% at 32–33 weeks' (moderate pre maturity), and 60–70% at 34–36 weeks' (near term) [158]. Preterm birth can also be classified in spontaneous preterm birth (births that follow spontaneous labour or premature rupture of membranes) or medically indicated preterm birth (where a medical or obstetrical condition exists that places the mother or the fetus at risk) [159].

2.3.2.2. Epidemiology of preterm birth

Preterm birth rate has been increasing in many countries. In 2005, it was estimated that 12.9 million births (9.6% of all births worldwide), were preterm. Approximately 85% of these preterm births were concentrated in Africa and Asia, while about 0.5 million occurred in Europe and North America and 0.9 million in Latin America and the Caribbean. The highest rates of preterm birth are in Africa and North America (11.9% and 10.6% of all births, respectively), and the lowest were in Europe (6.2%) [160]. The incidence of preterm birth in Canada increased from 6.6% of live births in 1991, to 7.6% in 2000 [161]. In 2008, the prevalence of preterm birth in Canada was 8.2% [162].

About 30–35% of preterm births are indicated, 40–45% follow spontaneous preterm labour, and 25–30% follow premature rupture of membranes (PROM) [158]. Spontaneous preterm birth is most commonly caused by preterm labour in white women, but by PROM in black women [163]. Risk factors for

preterm birth are multifactorial and vary by gestational age, geographic and ethnic contexts. Predictors for preterm birth include diverse maternal factors and clinical diagnoses [159, 161]. The clinical diagnoses that predispose to preterm delivery may be obstetrical (pre-eclampsia, placental abruption, placenta previa or polyhydramnios) or medical (diabetes and hypertension) [161, 164]. A short interpregnancy interval also increases the risk of preterm delivery [165-167]. Other maternal factors include low socioeconomic status, low body-mass index (BMI), age, stress, smoking, and a history of preterm birth, or of induced abortion [159, 164, 168]. In addition, there is increasing evidence of the association between maternal infections and preterm delivery [169-171].

2.3.2.3. Consequences of preterm birth

Premature children have higher rates of cerebral palsy, sensory deficits, learning disabilities and respiratory illnesses compared with children born at term [83]. The morbidity associated with preterm birth often extends to later life, resulting in enormous physical, psychological and economic costs [172]. Estimates indicate that in 2005 the costs to the United States in terms of medical and educational expenditure and lost productivity associated with preterm birth were more than US$ 26.2 billion [173]. Of all early neonatal deaths (deaths within the first 7 days of life) that are not related to congenital malformations, 28% are due to preterm birth [160].

2.3.2.4. Interventions for preterm birth

Interventions to reduce the morbidity and mortality related to preterm birth can be classified as primary (directed to all women before or during pregnancy), secondary (aimed to eliminate or reduce the risk in women with known risk

factors), or tertiary (initiated after the parturitional process has begun, with a goal of preventing delivery or improving outcomes for preterm infants) [174].

Most interventions intended to reduce preterm birth do not show consistent benefit when tested rigorously in randomized trials. A recent review has highlighted the evidence for interventions directed addressed to the mother [175]. Approximately 2000 studies were evaluated, and only 2 specific interventions were found to be effective in preventing preterm birth: smoking cessation and progesterone therapy for women at higher risk. A recent Cochrane review demonstrated that smoking cessation during pregnancy reduced preterm birth (RR= 0.86, 95% CI: 0.74-0.98) [176]. An extensive review of these interventions is beyond the scope of this thesis. Table 4 summarizes main interventions for preterm birth [83, 174, 177, 178].

Table 4. Interventions for preterm birth.

	Type of intervention	Comments
	Primary interventions	
Pre-conceptional primary prevention	• Public educational interventions. • Public and professional policies. • Nutritional supplementation for women planning their pregnancy. • Smoking cessation programs.	• Some authors consider these strategies attractive because many risk factors are difficult to address during pregnancy. • Primary prevention is an increasingly compelling strategy as the limitations of tertiary care become evident.
Primary prevention during pregnancy	• Nutritional / multivitamins supplements during pregnancy. • Smoking cessation programs adressed for pregnant women. • Prenatal care. • Periodontal care. • Screening of low-risk women.	• Screening for asymptomatic bacteriuria, cervicovaginal fetal fibronectin, and ultrasonographic measurement of cervical length.

Continuation of Table 4

Secondary interventions		
Pre-conceptional interventions	• Obstetric history of previous preterm birth.	• These interventions are addressed to women with evident risk of preterm birth on the basis of either obstetric history or present other risk factors.
Post-conceptional interventions	• Secondary prevention of indicated preterm birth. • Secondary prevention of spontaneous preterm birth. • Modification of maternal activity. • Nutritional supplementation. • Improved care for women at risk. • Antibiotic treatment. • Progesterone treatment. • Cervical cerclage.	• There is controversy over antibiotic treatment in women with a previous preterm birth who are reported to have bacterial vaginosis.
Tertiary interventions		
Tertiary interventions for women with immediate risk of preterm birth	• Early diagnosis of preterm labour. • Treatment of women with acute risk of preterm birth. • Tocolysis. • Care after preterm premature rupture of the fetal membranes. • Care after acute treatment for preterm labour. • Delivery of preterm infants.	• These interventions are based n the detection of conditions proximate to preterm birth such as uterine contractions, rupture membranes, and vaginal spotting or bleeding.

2.3.2.5. Role of maternal infections in the genesis of preterm birth

Preterm labour is now thought to be a syndrome initiated by multiple mechanisms, including infection or inflammation, uteroplacental ischaemia or haemorrhage, uterine overdistension, stress, and other immunologically mediated processes [158]. An ascending infection from the lower genital tract is thought to be the source of most intrauterine infections [179]. Once bacteria are in contact with placental tissues, a pro-inflammatory response can be initiated which leads to preterm labour. The inflammatory mediators implicated in preterm birth include interleukin-1b, interleukin-6, interleukin-8 and tumour necrosis factor-alpha [180, 181]. Other important inflammatory mediators of infection-induced preterm labor include prostaglandins and matrix metalloproteinases, which enhance myometrial contractility and weaken the collagen structure of the membranes, respectively [182]. Human studies in pregnant women have not adequately clarified a temporal relationship between these inflammatory mediators and the onset of preterm birth. This would allow the study of the pathophysiology of preterm birth and lead to opportunities for preventative and therapeutic discovery [83].

2.3.2.6. Anti-infective treatment as intervention to prevent preterm birth

During the last 20 years, several trials and observational studies were conducted to evaluate the efficacy of the interventions based on the use of anti-infective drugs to prevent preterm birth. These interventions can be classified as follows: I- Anti-infective treatment for preventing preterm birth with intact membranes in women with or without BV and II- Anti-infective treatment for preventing preterm birth in pregnant women with preterm premature rupture of membranes (PPROM).

In 1989, Newton et al. conducted one of the first studies addressing the use of anti-infective agents to prevent preterm birth in pregnant women with intact membranes [183]. The authors compared the efficacy of adjunctive therapy with intravenous ampicillin plus oral erythromycin in 103 women requiring parenteral tocolysis and with intact membranes. Compared with the placebo group, the adjunctive antibiotic group had a similar frequency of preterm birth (38% versus 44%), time to delivery (34 versus 34 days), and episodes of recurrent labor requiring parenteral tocolysis (0.43 versus 0.49). However, no significant benefit of this intervention in reducing the risk of preterm birth was demonstrated (RR= 0.84, 95%CI: 0.52-1.36).

Use of erythromycin and ampicillin was further evaluated in three different trials conducted by Eschenbach et al., [184], Newton et al. [185] and Romero et al., [186]. In the first study, pregnant women infected with *Ureaplasma urealyticum* were randomized to receive 333 mg of erythromycin or placebo three times daily, starting between 26 and 30 weeks' gestation and continuing through 35 completed weeks. There were no significant differences between erythromycin and placebo-treated women in gestational age at delivery (RR= 1.02, 95%CI: 0.70-1.48). Furthermore, there were no significant differences between erythromycin and placebo-treated women in infant birth weight, frequency of premature rupture of membranes, or neonatal outcome.

Same results were found in the second trial [185]. No differences were noted between placebo (n= 43) and study patients (n= 43) in gestational age at delivery, term deliveries, or neonatal outcome. Adjunctive ampicillin-sulbactam with indomethacin did not decrease the risk of preterm birth (RR= 0.85, 95%CI: 0.59-1.22). The third trial enrolled 277 women with singleton pregnancies and preterm labor with intact membranes (24 to 34 weeks), and randomly allocated them to receive either antibiotics or placebo (n= 133 for antibiotics group vs n= 144 for placebo group). No significant difference

between the treatment group and the placebo group was found in maternal outcomes, including duration of randomization-to-delivery interval, frequency of preterm delivery (< 37 weeks), frequency of preterm premature rupture of membranes, clinical chorioamnionitis, endometritis, and number of subsequent admissions for preterm labor. The authors concluded that there is no support the routine use of antibiotic administration to women in preterm labor with intact membranes (RR= 1.02, 95%CI: 0.82-1.29).

Intravenous treatment with another beta-lactam drug, mezlocillin in association with and erythromycin was compared to tocolytic treatment in women in preterm labor [187]. Women in the antibiotic group had a significantly lower incidence of postpartum infections compared with women in the placebo group. However, the study did not show antibiotic effect on the gestational age at delivery (RR= 0.87, 95%CI: 0.49-1.52).

In a prospective, randomized, double-blinded, placebo-controlled trial, Gordon et al. [188] determined the effect of ceftizoxime in the prolongation of 117 pregnancies receiving tocolysis for preterm labor. The groups consisted of women receiving either 2 g of ceftizoxime (n= 58) or a placebo (n= 59) every 8 hours. The primary end point of this study was prolongation of gestation. The authors found no effect of ceftizoxime on time to delivery or duration of pregnancy in women treated for preterm labor (RR= 1.05, 95%CI: 0.77-1.42).

Cox et al. [189] assessed the efficacy of ampicillin-sulbactam and amoxicillin-clavulanic acid in women hospitalized for preterm labor between 24 and 34 weeks of gestation. Thirty-nine women with preterm labor received antimicrobial therapy and 39 received placebos. The mean gestational ages at delivery were 34.2 +/- 0.7, for the treatment group and 34.1 +/- 0.6 weeks for the placebo group. The authors concluded that treatment with ampicillin-

sulbactam and amoxicillin-clavulanic acid is ineffective in the prevention of preterm birth (RR= 1.05, 95%CI: 0.71-1.53).

The effect of amoxicillin was further investigated in another trial conducted by Oyarzún et al. [7]. The authors randomly allocated 196 women with singleton pregnancies and preterm labor with intact membranes (22-36 weeks) to receive antibiotics or placebo, plus adjunctive parenteral tocolysis. From this total, 173 patients (treatment group n= 83 vs. placebo group n= 90) completed the treatment. The use of amoxicillin and erythromycin in association did not prolong pregnancy in patients with preterm labor and intact membranes (RR= 0.92, 95%CI: 0.67-1.25).

The ORACLE II trial, conducted by Kenyon et al., [190], randomly assigned 6295 women in spontaneous preterm labour with intact membranes to receive 250 mg of erythromycin (n= 1611), 325 mg of co-amoxiclav (n= 1550), both (n= 1565) or placebo (n= 1569) four times daily for 10 days or until delivery, whichever occurred first. Intention to treat analysis did not show benefit of treatment in the prevention of preterm birth (RR= 1.0, 95%CI: 0.93-1.08). The previous ORACLE I trial showed a decreased risk of preterm birth in women exposed to erythromycin [191]. However, contrary to the participants in the ORACLE II, women enrolled in the ORACLE I trials had PPROM. At that time, the ORACLE trials and were the largest and most ambitious perinatal trials ever funded and results clearly indicated that only women with PPROM would benefit from therapy.

In 1994, Norman et al. [192] conducted the first trial showing the benefit of treatment with antibiotics to prevent preterm birth in women with intact membranes. The study group (n= 43) received ampicillin and metronidazole for five days. The control group (n=38) received no antibiotics. In those receiving ampicillin and metronidazole the pregnancy was significantly

prolonged (median 15 days versus 2.5 days, p= 0.04) with significantly more women still pregnant after seven days (63% *versus* 37%, p= 0.03). In this study, the adjuvant use of ampicillin and metronidazole in the management of women in preterm labour significantly prolonged duration of pregnancy (RR= 0.34, 95%CI: 0.13-0.94). In that same year, Morales et al. also showed benefit of treatment with 250 mg of metronidazole in 44 women diagnosed with BV and with preterm birth in preceding pregnancy (RR= 0.41, 95% CI: 0.20-0.85) [193]. Compared to the placebo group, patients in the metronidazole group had significantly fewer hospital admissions for preterm labor (27% *versus* 78%), preterm births (18% *versus* 39%) and premature rupture of membranes (5% *versus* 33%).

The potential benefit of metronidazole showed by these studies leaded to the conduction of several trials that evaluated the efficacy of this drug during gestation. In 1995, Hauth et al. [194] randomized 624 pregnant women with BV to receive treatment with metronidazole plus erythromycin (n= 433) or placebo (n= 191) during the second trimester of gestation. Twenty-six percent of women assigned to metronidazole and erythromycin delivered prematurely, as compared with 36% assigned to placebo (p= 0.01). However, the association between the study treatment and lower rates of preterm birth was observed only among women with BV (RR= 0.72, 95%CI: 0.56-0.93).

Another double-blind controlled trial with 112 women conducted by Svare et al., showed the same results when eight days intravenous and oral treatment with metronidazole was used in association with ampicillin [195]. When compared to placebo, treatment was associated with a significant prolongation of pregnancy (admission to delivery 47.5 days *versus* 27 days, p < 0.05), higher gestational age at delivery (37 weeks *versus* 34 weeks, p < 0.05, RR= 0.65, 95%CI: 0.46-0.94), and decreased incidence of preterm birth (42% *versus* 65%, p < 0.05).

However, more recent trials that evaluated use of metronidazole alone did not show evidence of benefit. In 1997, McDonald et al. designed a multicentre, randomised, placebo-controlled trial to ascertain whether metronidazole treatment (400 mg, twice daily for two days) of 879 women with *Gardnerella vaginalis* during mid-pregnancy would reduce the risk of spontaneous preterm birth [196]. Intention-to-treat analysis showed no difference between metronidazole and placebo groups in overall preterm birth (7.2% *versus* 7.5%) or spontaneous preterm birth (4.7% *versus* 5.6%). Among 480 women with BV, treatment had no effect on spontaneous preterm birth (4.5% *versus* 6.3%). In the subgroup of women with a previous preterm birth, the use of metronidazole was associated with a significant reduction in spontaneous preterm birth (9.1% *versus* 41.7%, RR= 0.14, 95% CI: 0.01-0.84). A treatment effect was also found in compliant women with a previous preterm birth and BV. The authors concluded that treatment did not reduce the preterm birth rate in women with BV (RR= 0.97, 95%CI: 0.60-1.55). Nevertheless, these results suggested that benefit could be obtained with treatment of women with a previous preterm birth.

Carey et al. [197] conducted one of the largest trials at that time (n= 1953), and showed no evidence of benefit with 2 g metronidazole treatment of pregnant women with asymptomatic BV in the reduction of preterm birth rates (RR= 0.97, 95%CI: 0.60-1.55). However, BV resolved in 77.8% of women who had follow-up Gram's staining in the metronidazole group, and in 37.4% of women in the placebo group. The same team also showed in another trial, that pregnant women diagnosed with asymptomatic trichomoniasis had an 80% increase in the risk of preterm birth after use of metronidazole treatment, when compared to placebo [198]. The authors randomly assigned 617 women with asymptomatic trichomoniasis who were 16 to 23 weeks pregnant to receive two doses of metronidazole (320 women) or placebo (297 women) 48 hours apart. The infection resolved in 92% women in the metronidazole

group and in 35% of women in the placebo group. However, delivery occurred before 37 weeks of gestation in 19% of women in the metronidazole group and in 10% of women in the placebo group (RR= 1.8, 95% CI: 1.2 - 2.7).

Faillure of metronidazole to prevent preterm birth was also demonstrated by Odendaal et al. [199] (RR= 1.64, 95%CI: 1.06-2.53), Andrews et al. [200] (RR= 0.99, 95%CI: 0.71-1.38) and Shennan et al., in the PREMET study [201]. In this former trial, 900 pregnant women with at least one previous risk factor for preterm delivery (including mid-trimester loss or previous preterm delivery, uterine abnormality, cervical surgery or cerclage) were screened for fetal fibronectin at 24 and 27 weeks of gestation. Positive cases were randomised to a week's course of oral metronidazole or placebo. Primary outcome was delivery before 30 weeks of gestation. Secondary outcomes included delivery before 37 weeks. 21% of women receiving metronidazole delivered before 30 weeks compared with 11% taking placebo (RR= 1.9, 95% CI: 0.72-5.09). There were significantly more preterm deliveries (before 37 weeks) in women treated with metronidazole (62%) than women treated with placebo (39%) (RR= 1.6, 95% CI: 1.05-2.4).

Topical treatment of BV with clindamycin was evaluated in 8 clinical trials. In the first study conducted by McGregor et al. [202] use of clindamycin increased the risk of preterm birth, when compared to placebo (RR= 2.07, 95%CI: 0.73-5.84). Joesoef et al. [109] and Klebanoff et al. [203] also did not find any reduction in the risk of preterm birth after the use of this anti-infective (RR= 1.11, 95% CI: 0.77-1.61) and (RR= 0.91, 95% CI: 0.64-1.30), respectivelly. Vermeulen et al. [111] showed that prophylactic administration of clindamycin did not reduce the incidence of spontaneous preterm birth in women with an increased risk of recurrence (RR= 1.31, 95% CI: 0.76-.2.24). Same results were found by Kurkinen-Räty et al. [204] (OR 2.5, 95% CI: 0.6-

10), and by Kekki et al. [205] (RR= 1.29, 95%CI: 0.49-3.40). Most recent evidence from two larger trials did not corroborate the findings of previous studies. In 2003, Lamont et al. showed that 2% clindamycin vaginal cream administered to women with abnormal genital tract flora before 20 weeks of gestation, can reduce the incidence of preterm birth by 60%, when compared with placebo (RR= 0.41, 95% CI: 0.18-0.91) [110]. Benefit was also demonstrated by Ugwumadu et al. [206]; asymptomatic women with abnormal vaginal flora and BV treated with oral clindamycin early in the second trimester of pregnancy, had reduced rates of spontaneous preterm birth (RR= 0.61, 95%CI: 0.35-1.04). Current consensus is that topical intra-vaginal treatment with this agent is not recommended during pregnancy.

Two systematic reviews and meta-analyses concluded that treatment of BV is effective in eradicating infections, but there is no evidence to support the use of anti-infective treatment for BV or *Trichomonas vaginalis* in pregnancy to reduce the risk of preterm birth or its associated morbidities [107, 207]. The review conducted by Okun et al. [207] included results of 14 studies. The authors pooled the data from 5 trials and concluded that treatment is effective in eradicating infection (RR= 0.32, 95% CI: 0.20-0.52). However, there was no difference between the treatment and placebo groups on the risk of preterm birth at less than 37 weeks (RR= 0.93, 95% CI: 0.70 –1.22). The Cochrane review conducted by McDonald et al. [107] included 15 trials, involving 5888 women. Treatment was effective at eradicating BV during pregnancy (OR= 0.17, 95% CI: 0.15 - 0.20). Treatment did not reduce the risk of preterm birth before 37 weeks (OR= 0.91, 95% CI: 0.78-1.06)

Nevertheless, treatment before 20 weeks' gestation may reduce the risk of preterm birth less than 37 weeks (OR= 0.72, 95% CI: 0.55 - 0.95). The authors also showed that in women with a previous preterm birth, treatment

did not affect the risk of subsequent outcome (OR= 0.83, 95% CI: 0.59 - 1.17).

If treatment does not seem to be effective in women with intact membranes or BV, King et al. [208] suggested that further research may be justified in order to determine if there is a subgroup of women who could experience benefit from anti-infective treatment for preterm labour, and to identify which antibiotic or combination of antibiotics is the most effective. In 2010, Keynon et al. updated the results of a previous Cochrane review and meta-analyses in which the authors evaluated the immediate and long-term effects of administering anti-infective drugs to a sub-group of women with PROM [209]. This review included 22 trials, involving 6800 women and babies. The use of anti-infective drugs for PROM was associated with statistically significant reductions in chorioamnionitis (RR= 0.66, 95% CI: 0.46-0.96), and a reduction in the numbers of babies born within 48 hours (RR= 0.71, 95% CI: 0.58 - 0.87) and seven days of randomisation (RR= 0.79, 95% CI: 0.71-0.89). Therefore, women with PROM clearly benefit from therapy, compared to women with intact membranes. Furthermore, the following markers of neonatal morbidity were reduced: neonatal infection (RR= 0.67, 95% CI: 0.52-0.85), use of surfactant (RR= 0.83, 95% CI: 0.72-0.96), oxygen therapy (RR= 0.88, 95% CI: 0.81-0.96), and abnormal cerebral ultrasound scan prior to discharge from hospital (RR= 0.81, 95% CI: 0.68-0.98). However, the use of some agents (Co-amoxiclav) was associated with an increased risk of neonatal necrotising enterocolitis (RR= 4.72, 95% CI: 1.57-14.23). Given these results, the authors conclude that the benefits in some short-term outcomes should be balanced against a lack of evidence of benefit for others, including perinatal mortality, and longer-term outcomes.

Data from observational studies resulted in the same findings for most of the classes of anti-infected investigated in RCTs. In 2001, Larsen et al.

conducted a retrospective cohort study of birth outcome following gestational exposure to pivmecillinam, using data from the Prescription Database and the Birth Registry of Denmark [210]. The authors found no significantly increased risks for preterm delivery (OR= 0.91, 95% CI: 0.11-1.86).

The same drug was further evaluated in another cohort study designed by Vinther-Skriver et al. [211]. The authors used population-based registries in North Jutland County, Denmark of 63 659 women with a live birth, or stillbirth after the 28th week of gestation. 2031 women had redeemed prescriptions for pivmecillinam any time during pregnancy, 559 in the first trimester and 371 before delivery. Use of pivmecillinam during pregnancy did not appear to increase the risk of preterm delivery (RR= 0.96, 95% CI: 0.79-1.18), which corroborates previous data on this agent. However, this study lacked statistical power.

Another retrospective cohort study of maternal use of amoxicillin was conducted by Jepsen et al. Analyzing data of 401 primiparous women who redeemed a prescription for amoxicillin during their pregnancy, the authors did not find any increase in the risk of preterm birth after exposure (RR= 0.77, 95% CI: 0.49-1.21) [120]. Lack of evidence for amoxycillin/clavulanic acid was also detected in a cohort study conducted in Israel by Berkovitcz et al. [123]. In this study, the exposed group (n= 191) was composed of women treated with amoxycillin/clavulanic acid during the first trimester of pregnancy, and recruited from two teratogen information centres in Israel. Women were matched for age, smoking habits and alcohol consumption with 191 controls exposed to amoxycillin only for similar medical indications. Results showed that treated women had the same mean gestational age at delivery when compared to women exposed to amoxicillin alone (39.4 ± 1.6 weeks versus 39.6 ± 1.6 weeks, p= 0.294).

2.3.2.7. Studies assessing the risk of preterm birth after exposure to anti-infective drugs

A population-based follow-up study conducted by Dencker et al., in the county of North Jutland, Denmark, analyzed birth outcome of 1886 pregnancies that redeemed prescriptions for phenoxymethylpenicillin during pregnancy. No significantly increased risk of preterm birth was found (RR= 0.83, 95% CI: 0.66-1.04) [212].

The impact of cefuroxime use during the first trimester of pregnancy on the mean gestational age at delivery was evaluated by Berkovitch et al. in a prospective cohort study of 106 pregnant women recruited from three teratogen information centres in Israel [122]. After matching for age, smoking habits and alcohol consumption, no difference was observed between exposed and non-exposed group (39 ± 2.8 weeks versus 39 ± 1.7 weeks, p= 0.6). Use of cefuroxime and amoxycillin/clavulanic acid was further investigated by Benyamini et al. in a prospective cohort of 105 pregnant women [213]. Results did not indicate any significant difference in mean gestational week of birth in a cohort of women (39.79 ± 1.43 weeks for women exposed to amoxycillin/clavulanic *versus* 39.9 ± 1.28 weeks for women exposed to cefuroxime).

Sorensen et al., using data from the North Jutland Pharmacoepidemiological Prescription Database in Denmark, studied risk of prematurity after exposure to fluconazole [214]. The authors analyzed information on birth outcomes of 165 women who had taken fluconazole just before or during pregnancy. The study showed no increased risk of preterm birth in offspring of women who had used single dose fluconazole before conception or during pregnancy (OR= 1.17, 95% CI: 0.63-2.17). The same agent was studied by Mastroiacovo et al. in a prospective cohort study of women who contacted

three Italian teratogen information services [157]. Pregnancy outcomes of 226 women exposed to fluconazole were compared to that of 452 women exposed to nonteratogenic agents, and no evidence of risk was detected (RR= 1.73, 95%CI: 0.60-4.97).

Safety of itraconazole, another anti-fungal anti-infective, was evaluated by a cohort study conducted in Italy by De Santis et al. [215]. The authors found no difference in preterm delivery rates between exposed and non-exposed groups (6.8% *versus* 7.9%, $p < 0.05$). However, in this study, exposure was assessed for the first trimester, instead of second or third trimester of gestation.

In Denmark, in a prospective cohort, among 87 women who redeemed a fluoroquinolone prescription at any time during the pregnancy, Wogelius et al. showed that the prevalence ratio of preterm birth was 1.4 (95% CI: 0.6-3.2) [216]. Similar results were found for this class in a retrospective cohort of 57 users of this anti-infective class designed by Larsen et al. (RR= 1.30, 95% CI: 0.30-5.30) [139]. Furthermore, Loebstein et al. [138] enrolled and followed-up 200 women exposed to these drugs and found similar results (RR= 0.92, 95% CI: 0.42–2.00). In addition, exposure to other quinolones was evaluated with data for 116 prospectively documented pregnancies from the European Network of Teratology Information Services. No evidence of increased risk of prematurity was demonstrated [136]. A recent meta-analysis with pooled data of these studies did not show evidence of increased risk of preterm birth after exposure to quinolones (OR= 1.15, 95% CI: 0.69–1.91) [217]. In an additional analysis including only fluoroquinolones (nalidixic acid was removed), the summary odds ratio for major malformations remained non-significant (OR= 1.11, 95% CI: 0.57–2.15).

The association between use of sulfamethizole and preterm birth was investigated in a case-control study conducted by Ratanajamit et al. [135] There was no increase in the risk of preterm birth after exposure during pregnancy (OR= 1.12, 95%CI: 0.97-1.30). In another study conducted by Sarkar et al., [127] gestational exposure to azithromycin was not related to preterm birth in a cohort of 123 pregnant women (p= 0.76). Similar results were found in a cohort of pregnant women infected with *Chlamydia trachomatis* [218]. In this study, the grouped treated only with azithromycin had a non-significant higher incidence of preterm delivery when compared to the group exposed to erythromycin (7.5% versus 4%, p=0.54). Similar results were found for another macrolide drug: exposure to roxithromycin in a cohort of pregnant women was not associated to preterm birth (mean gestational age at delivery was 39.2 weeks in the exposed group and 39.4 in non-exposed women (p= 0.6)).

Sorensen et al. [214] did not show any evidence of an increase in the risk of preterm delivery after exposure to metronidazole in a cohort study of 124 pregnant women using data from the North Jutland Pharmacoepidemiological Prescription Database (OR= 0.80, 95%CI: 0.35–1.83). Exposure to metronidazole [153] and mebendazole [219] was evaluated with data from the Israeli Teratogen Information Service, and no evidence of increased risk of preterm birth was found.

The impact of prenatal antibiotics used in addition to those used to treat group B streptococcal bacteriuria was assessed by Anderson et al. using data from hospital files [220]. In this study, the frequency of preterm birth was 16% among women in the control group, 16% for women with bacteriuria not receiving additional antibiotics, and 28% for women with bacteriuria who received antibiotics. Among women with bacteriuria, the risk of preterm birth was increased (OR= 2.7, 95% CI: 1.2-6.1).

A Cochrane review, one meta-analyses and a systematic review summarized most of the evidence available from RCTs of interventions for preventing and treating preterm birth. The Cochrane review showed a reduction in maternal infection with the use of prophylactic antibiotics (RR= 0.74, 95% CI: 0.64-0.87). However, no clear overall benefit from prophylactic antibiotic treatment for preterm labour with intact membranes was obtained (RR= 1.22, 95% CI: 0.88-1.70) [208]. The meta-analysis conducted by Simcox et al. [221] concluded that there was no significant association between antibiotic treatment and reduction of preterm birth irrespective of criteria used to assess risk, the anti-infective drug used, or gestational age at time of treatment (RR= 1.03, 95% CI: 0.86-1.24).

In summary, the arguments in favour of anti-infective treatment of women with underlying risk factors emphasise the need for clindamycin oral treatment in women symptomatic for BV before 20 weeks' gestation [222]. Support for treatment originated from secondary analyses of the trial conducted by Hauth et al. in women at risk of preterm birth, in which benefit was limited only to women with BV, and from another trial conducted by McDonald et al. in which benefit was limited to those women with a diagnosis for BV and with previous preterm birth [194, 196]. However, clinicians should be aware that intravaginal clindamycin cream might be associated with adverse outcomes if used in the latter half of pregnancy [32].

Arguments against antibiotic treatment are based on the increased incidence of preterm birth in women given metronidazole, found by Andrews et al., Klebanof et al. and in the PREMET study [200, 201, 203]. In addition, the Cochrane review conducted by McDonald et al. corroborates the findings of a negative effect of treatment [107]. Although anti-infective treatment can eradicate BV in pregnancy, it does not reduce the risk of preterm birth or

PROM before 37 weeks' gestation in all women or in those with a previous preterm birth.

There is less controversy when considering the use of antibiotics to reduce the risks of adverse feto-maternal outcome following PROM. When compared with placebo, antibiotics reduce the rate of delivery within 48 hours and delivery within seven days [222, 223].

A summary of the observational studies and meta-analysis of RCTs, assessing anti-infective treatment during pregnancy and the risk of preterm birth is presented in Table 5.

Table 5. Summary of the studies on the association between the use of anti-infective drugs during pregnancy and the risk of preterm birth.

Authors, year and country	Study design	Class or type of anti-infective drug	Number of exposed subjects (prevalence of outcome)	Exposure window	Outcome of interested	Measure of effect (RR, OR or P values)
Beta-Lactams						
Berkovitch et al., 2000, Israel [123]	Prospective cohort study	Cefuroxime	109 (4.3%)	First trimester of gestation	Delivery before 37 weeks of gestation	RR= 0.70 (0.20-2.39)
Larsen et al., 2001, Denmark [210]	Retrospective cohort study-Administrative database	Pivmecillinam	411 (7%)	All gestational period	Delivery before 37 weeks of gestation	OR= 0.91 (0.11-1.86)
Dencker et al., 2002 [212]	Case-control study	Phenoxy-methyl-penicillin	2540 (5.5%)	All gestational period	Delivery before 37 weeks of gestation	OR= 0.83 (0.66-1.04)

Jepsen et al., 2003, Denmark [120]	Case-control study- Administrative database	Amoxicillin	401 (7.5%)	All gestational period	Delivery before 37 weeks of gestation	OR= 0.77 (0.49-1.21)
Berkovitch et al., 2004, Israel [122]	Prospective cohort study	Amoxycillin/ clavulanic acid	163 (3.8%)	First trimester of gestation	Delivery before 37 weeks of gestation	OR= 1.24 (0.39-3.97)
Vinther-Skriver et al., 2004, Denmark [211]	Case-control study - Administrative database	Pivmecillinam	2031 (7%)	First trimester of gestation and 1 month before delivery	Delivery before 37 weeks of gestation	OR= 0.96 (0.79-1.18)
			Macrolides			
Rahangdale et al., 2006, USA [218]	Retrospective cohort study - Administrative database	Azithromycin	221 (7.5%)	Exposure during the third trimester of gestation	Delivery before 37 weeks of gestation	P= 0.54
Sarkar et al., 2006, Canada [127]	Retrospective cohort study - Administrative database	Azithromycin	123	All gestational period	Gestational age at birth in weeks	P= 0.67

Morency and Bujold, 2007, Canada [224]	Systematic review / Meta analysis	Macrolides	1817	Second and third trimester of gestation	Delivery before 37 weeks of gestation	OR= 0.72 (0.56-0.93)

Quinolones

Berkovitch et al., 1994, Canada [36]	Retrospective cohort study - Administrative database	Norfloxacin and ciprofloxacin	38 (19%)	First trimester of gestation (94% of cases)	Delivery before 37 weeks of gestation	P= 0.7
Schaefer et al., 1996, Germany [136]	Prospective follow-up study	Quinolones	15 (3.6%)	First trimester of gestation	Delivery before 37 weeks of gestation	Not reported
Loebstein et al., 1998, Canada [138]	Prospective cohort study - Administrative database	Quinolones	200	All gestational period	Delivery before 37 weeks of gestation	RR= 0.92 (0.42–2.00)

Larsen et al., 2001, Denmark [139]	Retrospective cohort study - Administrative database	Fluoro-quinolones	57 (8.8%)	All gestational period	Delivery before 37 weeks of gestation	RR= 1.53 (0.62-3.80)
Wogelius et al., 2005, Denmark [216]	Case-control study - Administrative database	Fluoro-quinolones	217	All gestational period	Delivery before 37 weeks of gestation	OR= 1.4 (0.6-3.2)
Bar-Oz et al., 2009, Israel [217]	Meta-analysis of Observational studies	Quinolones	984 (27%)	All gestational period	Delivery before 37 weeks of gestation	OR= 1.05 (0.90-1.22)

Urinary anti-infectives

Ratanajamit et al., 2003, Denmark [135]	Case-control study - Administrative database	Sulfa-methizole	3484 (8%)	30 days before conception	Delivery before 37 weeks of gestation	OR= 1.12 (0.97-1.30)

Metronidazole and azoles

Mastroiacovo et al., 1995, Italy [157]	Prospective cohort study	Fluconazole	226	First trimester of gestation	Delivery before 37 weeks of gestation	RR= 1.73 (0.60-4.97)

Sorensen et al., 1999, Denmark [214]	Case-control study- Administrative database	Fluconazole	301 (6.6%)	All gestational period	Delivery before 37 weeks of gestation	OR= 1.17 (0.63-2.17)
Diav-Citrin et al., 2001, Israel [153]	Retrospective cohort study	Metro-nidazole	228 (6.8%)	First trimester of gestation	Delivery before 37 weeks of gestation	P= 0.58
Diav-Citrin et al., 2003, Israel [219]	Retrospective cohort study	Mebendazole	192	All gestational period	Median gestational week at delivery	P= 0.65
De Santis et al., 2009, Italy [215]	Prospective cohort study	Itraconazole	206 (6.8%)	First trimester of gestation	Delivery before 37 weeks of gestation	Not disclosed (NS)

Others

King and Flenady, 2002, Australia [208]	Systematic review / Meta analysis of RCTs	Prophylactic antibiotics for inhibiting preterm labour with intact membranes	5204 (7.6%)	Last two trimesters of gestation	Delivery before 37 weeks of gestation	OR= 2.7 (1.2-6.1)

Okun et al., 2005, Canada [207]	Systematic review / Meta analysis of RCTs	Antibiotics for BV treatment	3146 (13%)	Second and third trimester of gestation	Delivery before 37 weeks of gestation	RR= 0.93 (0.70 –1.22)
McDonald et al., 2007, Australia [107]	Systematic review / Meta analysis of RCTs	Antibiotics for BV treatment	5888 (12%)	Second and third trimester of gestation	Delivery before 37 weeks of gestation	OR= 0.91 (0.78 to 1.06)
Simcox et al., 2007, UK [221]	Systematic review / Meta analysis of RCTs	Clindamycin, metro-nidazole and erythromycin	4939 (14%)	Second and third trimester of gestation	Delivery before 37 weeks of gestation	RR= 1.03 (0.86-1.24)
Anderson et al., 2008, USA [220]	Retrospective cohort study	Additional antibiotics for women with GBS infection	120 (16%)	Third trimester of gestation	Delivery before 37 weeks of gestation	P= 0.04
Kenyon et al., 2010, UK	Systematic review / Meta analysis of RCTs	Antibiotics for premature rupture of membranes	3642 (13%)	Second and third trimester of gestation	Delivery before 37 weeks of gestation	RR= 1.00 (0.98-1.03)

2.3.3. Use of anti-infective drugs and the risk of infants born small for their gestational age

2.3.3.1. Definition of small for gestational age

The term small for gestational age (SGA) has been applied to newborns having a birth weight and/or a birth length below the 3rd or 10th percentile of birth weight for gestational age and sex, based on the distribution in a standard population (or below −1.88 or −1.29 standard deviation) [162]. Neonates with either low birth weight or length or both for gestational age should be considered SGA [225]. Although the definition is somewhat arbitrary, the common 10th percentile cut-off point for SGA is the most used criteria in the literature [226, 227].

The terms SGA, intrauterine growth restriction (IUGR) and low birth weight are often used interchangeably by obstetric and pediatric clinicians and in the literature [228]. Although there is considerable overlap between these conditions, these terms are not synonymous [225]. IUGR refers to fetal growth retardation and can be observed as a deviation of the intra-uterine growth chart. Therefore, IUGR can only be diagnosed when documented by two intrauterine growth assessments by ultrasound measurements [229]. Low birth weight is defined by the World Health Organization as weight at birth of less than 2500 g. However, this is very broad classification for international comparison of neonatal and public health, which includes premature infants, who though small, have a weight and length that is appropriate for their gestational age [230].

SGA does not refer to fetal growth but refers to body size at birth. Not all SGA infants have suffered from intrauterine growth retardations, as an SGA infant may have been small from the beginning of fetal life. Infants born SGA may be further classified as SGA-W (low birth weight), SGA-L (low birth length), or SGA-WL (low birth weight and length) [225].

2.3.3.2. Epidemiology of small for gestational age

By definition, approximately 10% of all pregnancies will result in newborns that are “too small”. Approximately 4% of all live born neonates are born SGA when SGA is defined as birth length or birth weight below 2 standard deviations of the distribution. There is a lack of data on the incidence of SGA births in many countries because birth length and gestational age are sometimes not recorded in national databases [225]. However, based on available data, it has been estimated that between 2.3% and 10% of all infants are born SGA [160, 162, 228], although this may still be an important underestimate in international terms [230]. In Canada, previous report indicate that the prevalence of SGA is 7.8% [162].

Risk factors and predictors for SGA should be identified given that underlying mechanisms are diverse and may influence prognosis and treatment effects [225]. SGA can be caused by demographic, fetal, maternal and placental factors [225].

Demographic factors include maternal race, obstetric history, age of the mother, height of the mother and father and multiple gestation. Pregnant women with more than 35 years have been found in several studies to have an elevated risk of SGA [230, 231]. Although the incidence of SGA neonates is higher among teenage mothers, it is unclear whether age alone or socio-economic factors are the cause [232]. Maternal race can also influence fetal growth. Studies demonstrate that Afro-American women have more chance to bear SGA infants than white American women [233]. Paternal characteristics including age, height, birth weight, and low levels of education are also associated with SGA [227].

Fetal risk factors include genetic and congenital defects, metabolic diseases and multiple gestations, and are responsible to 15% to 20% of SGA cases [234]. Among genetic defects, some karyotipic abnormalities such as trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome) and monosomy X (Turner syndrome) are responsible for 5 to 7% of all SGA births [86, 225, 229-231]. Approximately 38% of infants with chromosomal abnormalities are born SGA [230].

Maternal factors can be divided into medical conditions and maternal environmental factors. Medical complications include: chronic vascular diseases (secondary to conditions such as hypertension, diabetes mellitus or renal disorders), conditions associated with low perfusion (such as asthma, chronic anemia, sickle cell anemia, cyanotic heart disease, chronic pulmonary disease), infections (malaria, toxoplasmosis, trypanosomiasis and particularly viral infections such as rubella, cytomegalovirus, human immunodeficiency virus and herpes virus), and low pre-pregnancy weight and low pregnancy weight with poor weight gain during pregnancy [225, 230]. Environmental factors include: use of therapeutic drugs (antimetabolites, anticonvulsants, anticoagulants, folic acid antagonists), illicit drug use, alcohol abuse and cigarette smoking. Smoking is one of the most common environmental causes of SGA birth [226]. Smoking causes fetal oxygen deprivation, which can retard fetal growth and result in SGA [225, 226]. About 12% of children younger than age 2 whose mothers had smoked while pregnant had been SGA births, compared with only 4% whose mothers had not smoked [230].

Placental risk factors involve problems in placental perfusion. As the placenta is essential for nutrient and oxygen supply from mother to fetus, any placental dysfunction could result in SGA [230].

2.3.3.3. Consequences of infants born small for their gestational age

Infants born SGA are at increased risk of morbidity and mortality both in the perinatal period and in later life [230]. In the perinatal period, these complications include respiratory distress, hypotension, hypoglycemia, necrotizing enterocolitis, and neonatal death [235]. Subsequently, infants and children born SGA are more susceptible to neurological impairment, delayed cognitive development, and poor academic achievement [236, 237]. Adolescents and adults born SGA are at increased risk of developing cardiovascular disease, obstructive pulmonary disease, type II diabetes, renal insufficiency, and impaired reproductive function [238-240]. Failure to achieve appropriate catch-up growth after SGA birth results in persistent short stature and is associated with higher health risks and psychosocial impairment, compared with patients born SGA who achieve their growth potential [241, 242]. The exact consequences of SGA on the subsequent development of these infants depend on the specific cause giving rise to SGA, its time of occurrence and the duration of the impairment. As the burden is so significant, the detection and management of risk factors are crucial [234].

2.3.3.4. Role of maternal infections in the pathogenesis of small for gestational age

Infections are responsible for up to 5-10% of SGA cases [243]. There is emerging evidence that subclinical infection and inflammation may lead to chorioamnionitis, fetal growth restriction and SGA [244]. The most common causes of SGA are toxoplasmosis and cytomegalovirus, and they should be the ones most frequently tested for during pregnancy. Cytomegalovirus infection is associated with direct fetus cytolysis and loss of functional cells [245]. Some authors observed that first episodes of herpes simplex virus infection, especially during the third trimester, also may be associated with

impaired fetal growth [246]. Rubella causes vascular insufficiency by damaging the endothelium of small vessels and also reduces cell division [247]. However, due to widespread vaccination, rubella is less of a threat. Syphilis is still being diagnosed during in pregnancy both in developed and developing countries [244]. The disease results in marked vasculitis, mild thrombosis, and villous edema of the placenta. Malaria is the predominant infectious cause of SGA in Africa, South-East Asia, and other countries where malaria is endemic, accounting for 40% of cases of SGA [248]. The pathogenesis of malaria activates immune-mediated inflammatory processes, as well as platelets which become deposited in the vascular system and lead to vessel obstruction [248].

Some studies suggested that maternal UTIs, chlamydia and mycoplasma infections increase the risk of SGA [249]. Furthermore, systemic infection, such as advanced tuberculosis, may also be associated with fetal growth deficit [250]. Recent findings that maternal periodontal disease may lead to preterm and SGA births, indicates that infection is a modifiable etiologic factor; its treatment can potentially reduce the frequency of SGA [251, 252]. In a prospective longitudinal study, it was shown that pregnant women with higher levels of periodontal infection had increased risk of giving birth to low birth weight infants (OR= 4.1; 95% CI: 1.3–12.8) after controlling for smoking, age, and race [251].

The direct consequences of maternal infections is sub-optimal placental perfusion and a dysfunction of the placental microvascularity, which results in an inadequate maternal supply of oxygen and nutrients to the fetus and the consequent decreased ability of the fetus to use the supply [247].

2.3.3.5. Anti-infective drugs and the risk of small for gestational age

Very few studies assessed the risk of having an infant SGA after exposure to anti-infective drugs during pregnancy. Wen et al. conducted one of the most recent observational studies assessing maternal exposure to folic acid antagonists (such as sulfamethoxazole–trimethoprim) and the risk of SGA and other placenta-mediated adverse pregnancy outcomes [13]. Using data from health administrative database from Saskatchewan, Canada, the authors found that exposure to these drugs significantly increased the risk of SGA, when the outcome is defined as birth length smaller than the 3rd percentile (OR=1.22, 95% CI: 1.11–1.34), whereas a smaller association was found when SGA was defined as birth length smaller than the 10th percentile (OR=1.07, 95%CI: 1.01–1.13). Although some methodological flaws in this study, such as confounding by indication, the authors put their findings in perspective with a very strong biological rational: a placental microvascular disease may arise from a maternal folate-homocysteine metabolic defect caused by an exposure to these drugs. This could explain how sulfamethoxazole–trimethoprim is associated with the development of the events that lead to SGA newborns. Other possible related factors are the well-documented gastrointestinal adverse effects of this drug (nausea, vomiting, diarrhea and stomatitis) that could play a synergic role in preventing the fetus from receiving essential micronutrients from the mother.

The vast majority of studies that investigated this issue analyzed the risk of having a low birth weight child, instead of directly assessing IUGR or SGA. In addition, in most of these studies, low birth weight was not the principal outcome of interest, but rather a secondary outcome. A recent Cochrane review summarized the evidence of five RCTs with data on weight at birth after gestational exposure to anti-infective drugs [208]. After pooling results of 6628 subjects, the authors found no evidence of effect on birth weight after

use of anti-infective during pregnancy (RR= 1.04, 95% CI: 0.95-1.13). Same results were found when analysis were done within classes of anti-infective drugs; no increase in the risk was detected after use of betalactams antibiotics (RR= 1.08, 95% CI: 0.94-1.24), macrolides (RR= 1.05, 95% CI: 0.90-1.22), association of beta-lactams and macrolides (RR= 1.02, 95% CI: 0.87-1.20) and antibiotics active against anaerobic bacteria (RR= 0.75, 95% CI: 0.56-1.01).

Meta-analysis of two RCTs with data on 4876 pregnant women with PPROM, also showed that exposure to anti-infective drugs seems not to be associated with low birth weight (RR= 1.00, 95% CI: 0.96-1.04) [209]. Same results were found in another Cochrane review four RCTs that with data on 3151 pregnant women with a diagnosis of BV (RR= 1.00, 95% CI: 0.79-1.27) [107]. Among women with asymptomatic bacteriuria during pregnancy, the use of antibiotics was associated with a reduction in the incidence of low birth weight babies (OR= 0.60, 95% CI: 0.45 - 0.80) [253, 254].

A summary of the studies assessing anti-infective treatment during pregnancy and the risk of SGA is presented in Table 6.

Table 6. Summary of the studies on the association between the use of anti-infective drugs during pregnancy and the risk of SGA.

Authors, year and country	Study design	Class or type of anti-infective drug	Number of exposed subjects (prevalence of outcome)	Exposure window	Outcome of interested	Measure of effect (RR, OR or P values)
King and Flenady, 2002, Australia [208]	Systematic review / Meta analysis of RCTs	Prophylactic antibiotics for inhibiting preterm labour with intact membranes	4882	Last two trimesters of gestation	Birthweight < 2500 g	RR= 1.04 (0.95-1.13)
McDonald et al., 2007, Australia [107]	Systematic review / Meta analysis of RCTs	Antibiotics for BV treatment	1568 (9.3%)	Last two trimesters of gestation	Birthweight < 2500 g	RR= 1.00 (0.79-1.27)

Smail and Vasquez, 2007, Canada [254]	Systematic review / Meta analysis of RCTs	Antibiotic treatment for asymptomatic bacteriuria	764 (8.5%)	Last two trimesters of gestation	Birthweight < 2500 g	RR= 0.66 (0.49 - 0.89)
Wen et al., 2008, Canada [13]	Retrospective cohort study	Exposure to folic acid antagonists (Sulfa-methoxazole – trimethoprim)	14 982 (4%)	1-year period before delivery	Small-for-gestational age (Fetal growth restriction < 3rd percentile)	OR= 1.20 (1.08–1.32)
Kenyon et al., 2010, UK [209]	Systematic review / Meta analysis of RCTs	Antibiotics for premature rupture of membranes	3614	Last two trimesters of gestation	Birthweight < 2500 g	RR= 1.00 (0.96-1.04)

2.4. QUALITY APPRAISAL OF THE STUDIES THAT INVESTIGATED THE USE OF ANTI-INFECTIVE DRUGS DURING PREGNANCY AND THE RISK OF PRETERM BIRTH AND SGA

A critical appraisal of the studies described in the last sections indicates that, despite the amount of data available and the good methodological quality of some studies (such as the ORACLE trials [190, 191]), the evidence presented is inconclusive for most of the research questions. Due to a variety of factors, there is clinical controversy on anti-infective treatment during pregnancy to prevent preterm birth and SGA [174]. Trials and observational studies have reported conflicting results because of variation in timing, dose, choice of treatment and statistical power issues [111, 197, 200, 201].

One possible reason for the lack of benefit of treatment found in most of the observational studies and clinical trials, is the inappropriate exposure window chosen to evaluate the potential effect of treatment on preterm birth. If treatment is evaluated later in gestation, it might not be effective in preventing the inflammation of the fetal membranes due to BV or UTIs (chorioamnionitis), which leads to preterm delivery [174]. Two trials conducted by Goldenberg et al. and Ugwumadu et al. in 2006, reported no difference in histological chorioamnionitis between women randomly assigned antibiotics *versus* placebo late in gestation [249, 252]. In addition, this fact could be responsible for some reports of an increased risk of preterm birth after exposure to anti-infective treatment, which in fact, could be due to chorioamnionitis' severity instead of a real independent effect of treatment.

Another possible reason for treatment failure reported by some studies is that host factors, such as smoking habits, diet, and individual variations in inflammatory response, might influence the risk of preterm birth and SGA,

irrespective of the choice of anti-infective treatment. The observational studies reviewed in this thesis, barely had information on the first two host factors, whereas clinical trials were not able to control for the variations in inflammatory response between subjects. Most of the studies did not have information on exposure to other medications, comorbidities and other potential confounders, such as the access to health care by the subjects. More studies are needed to evaluate the effect of anti-infective drugs on the risk of SGA.

Statistical power is by far, the main limitation of the vast majority of trials analyzed. The small sample sizes in some trials are problematic when attempting to apply the results to the general population. In addition, information on exposure to different classes and individual anti-infective drugs is lacking in these studies. Furthermore, heterogeneity in pooling of data issued from these trials was demonstrated in a number of Cochrane reviews and meta-analysis [89, 90, 107, 207-209, 253]. For example, all reviews evaluating the effectiveness of anti-infective treatment for BV in pregnancy encountered significant heterogeneity.

There is a need of more evidence-based studies determining the independent effect of anti-infective drugs on adverse pregnancy outcomes [251], and that overcome these methodological drawbacks.

Chapter 3
OBJECTIVES

The objectives of the five manuscripts presented in this thesis are described bellow.

3.1. STUDY 1: PREVALENCE AND PREDICTORS OF ANTI-INFECTIVE DRUG USE DURING PREGNANCY

The objectives of this study were to:

- Measure the prevalence of anti-infective drug use before, during, and after the end of gestation.
- Describe the classes, types, and indications for anti-infective use during pregnancy.
- Identify and quantify predictors associated with anti-infective drug use during pregnancy.

3.2. STUDY 2: TRENDS IN ANTI-INFECTIVE DRUGS USE DURING PREGNANCY – A SHORT COMMUNICATION

The objective of this study was to:

- Describe trends in the use of general and broad-spectrum anti-infective drugs during pregnancy in the province of Quebec, Canada, over a period of five years.

3.3. STUDY 3: EXPOSURE TO ANTI-INFECTIVE DRUGS DURING PREGNANCY AND THE RISK OF PRETERM BIRTH

The objective of this study was to:

- Determine the association between anti-infective exposure during the second and/or third trimester of pregnancy and the risk of preterm birth, according to the class and type of anti-infective drug used.

3.4. STUDY 4: EXPOSURE TO ANTI-INFECTIVE DRUGS DURING PREGNANCY AND THE RISK OF SMALL-FOR-GESTATIONAL-AGE

The objective of this study was to:

- Determine the association between anti-infective exposure during the second and/or third trimester of pregnancy and the risk of small-for-gestational-age, according to the class and type of anti-infective drug used.

3.5. STUDY 5: RISKS AND BENEFITS OF THE USE OF METRONIDAZOLE DURING PREGNANCY: A REVIEW OF THE EVIDENCE

The objective of this study was to a synthesis of the available evidence on the association between metronidazole use during pregnancy and the risk of preterm delivery and birth defects.

Chapter 4
METHODS

4.1. DATA SOURCES

Data were obtained from the Quebec Pregnancy Registry, a population-based cohort of pregnant women built with the linkage of three administrative databases: the *Régie de l'assurance maladie du Québec* (RAMQ) database, the *Maintenance et exploration des donnés pour l'étude de la clientele hospitaliere* (Med-Echo) database, and the *Fichier des évenements démographiques de l'Institut de la statistique du Québec* (ISQ).

In Quebec, Canada, the RAMQ is the government body that administers the province's health matters. All healthcare services are recorded in the RAMQ administrative databases, which are comprised by a set of claims files. The RAMQ database (medical claim file and the pharmaceutical claim file) provides information on medical services dispensed to all Quebec residents and on prescriptions filled for residents insured by Quebec's Public Drug Insurance Plan. This database prospectively provides collected data on filled prescriptions, physician-based diagnoses (International Classification of Diseases, ninth revision, ICD-9) [255], therapeutic procedures, characteristics of the patient and health care providers, and the costs involved. The RAMQ covers the costs for medical services provided to all Quebec residents and the drug insurance plan insures approximately 50% of Quebec residents, which include persons of 65 years or older, welfare recipients and their children, and all workers and their families who do not have access to a private drug insurance program (adherents) [256]. Medications prescribed during hospitalization are not included in the database. Women insured by

the Quebec's Public Drug Insurance Plan are younger, more likely to be immigrant, and have a household income below poverty level. They are also less likely to be caucasian, employed, and have a post-secondary education. No differences were observed on smoking status and alcohol use during pregnancy, when compared to women with private insurance. Access to health care services between women covered for their medications by the Quebec's Public Drug Insurance Plan and those covered by private drug plans is similar [257].

Med-Echo is the Quebec hospital discharge database that has been put in place since 1980. The Med-Echo database records acute care hospitalization data for all Quebec residents (age, sex, admission diagnosis, up to 15 secondary diagnosis, duration of stay, dates of admission and discharge, type of hospital and services received during hospitalization). All diagnoses are coded according to ICD-9 system. The database also records gestational age for planned abortions, miscarriages and deliveries. Gestational age is defined from the first day of the last menstrual period to the end of pregnancy, and confirmed by ultrasound around the 18th-20th week of gestation.

The ISQ administers the *Fichier des événements démographiques* that provides data on all births and deaths in Quebec. The following demographic information is included: for the mother (date of birth, age, marital status, mother-tongue, place of birth, area of residence, number of live births, number of deliveries), for the father (date of birth, age, mother-tongue, place of birth); and for the baby (gender, type of delivery, weight, gestational age, order in the family, date of birth).

The linkage between RAMQ and Med-Echo data was possible using patients' *Numéro d'assurance maladie* [258], which is a unique identifier for all legal residents of Quebec. The mother-child linkage was possible using the unique

identifier that links each baby born in Quebec to his/her mother in the RAMQ database. The linkage between the RAMQ and ISQ was done using the first name, family name and date of birth of both the mother and child.

Data recorded in the RAMQ medication database have been formally evaluated and found to be comprehensive and valid [259]. Medical diagnoses and pregnancy related data recorded in the ISQ and Med-Echo databases have also been evaluated and found to be valid and precise (length of gestation, date of last menstruation, date of delivery, maternal age) [260].

The Quebec Pregnancy Registry currently contains data on all pregnancies that occurred in Quebec between January 1, 1997 and December 31, 2003 and were covered by Quebec's Public Prescription Drug Insurance Plan. The Registry cointains data on more than one pregnancy per women, if subjects were covered by the Quebec's Public Prescription Drug Insurance Plan during their different gestations. An update of the registry is currently underway to include medical, pharmaceutical and hospital data on new pregnancies, as well as follow-up data from 2003-2009 on mothers and children for pregnancies that are already present in the registry.

The Quebec Pregnancy Registry is a cohort of pregnant women built with the linkage of governmental health administrative database. The research team of Dr. Anick Berard at the St-Justine Research Centre conceived this cohort. It is not a governmental database. The use of the data was approved by the CHU Sainte-Justine Hospital Ethics Committee, and by the *Commission d'accès à l'information du Québec*, the provincial agency that grants authorization for the use of linked administrative databases.

4.1.1. Study population

The study population for the four first studies in this thesis was composed of all pregnant women that were insured by the Quebec's Public Drug Insurance Plan, and who filled at least one anti-infective prescription between January 1, 1997 and December 31, 2003. A total of 109 344 pregnant women had coverage by the RAMQ drug plane before and during gestation. The pregnancies were first identified by a prenatal visit in the RAMQ database or by a therapeutic procedure related to pregnancy in the RAMQ or Med-Echo files.

4.2. METHODS FOR STUDY 1 AND 2

4.2.1. Study design

For the study on the Prevalence and predictors of anti-infective use during pregnancy (Study 1) and Trends in anti-infective drug use (Study 2), a retrospective cohort study within the Quebec Pregnancy Registry was conceived.

4.2.2. Study population

The study population for these studies was selected from the study population described in the section 4.1.1 To be included in these studies, women had to meet the following eligibility criteria: (1) be between 15 and 45 years of age on 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 after the end of the pregnancy. The end of the pregnancy was defined as the calendar date of a planned abortion, miscarriage, or delivery. If

a woman had more than one pregnancy between 1998 and 2003, the first pregnancy meeting eligibility criteria was included for analysis.

4.2.3. Assessment of Exposure

For Study 1, anti-infective drugs were categorized using the 2008 Anatomical Therapeutic Chemical (ATC) classification index. Data were collected for oral systemic agents in the ATC subgroups J01 (anti-bacterial agents), J02 (anti-mycotics), and J04 (anti-mycobacterials).

For Study 2, trends in use were assessed for 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). For both studies, data on exposure was obtained in the pharmaceutical claims file of the RAMQ databases. The ATC classification system is widely used internationally for drug utilization studies, such as Study 1 [261]. Given that the RAMQ prescription files classifies drug information following the AHFS system, we decided to use this system to assess exposure in the Study 2.

4.2.4. Assessment of Outcome

In both studies, the prevalence of anti-infective drug use during the 12 months before pregnancy was calculated by dividing the number of women receiving at least one prescription for an anti-infective in this 12-month period by the total number of women that met eligibility criteria.

4.2.5. Covariates

The following variables were considered as potential predictors of receiving at least one anti-infective drug at the beginning of gestation: maternal age, maternal place of residence, maternal RAMQ drug plan status, calendar year of the pregnancy, number of different types of medications used other than anti-infective, number of different prescribers for all medications, planned abortions or miscarriages, number of visits to the physician, visits to the emergency department and/or hospitalizations, diabetes, asthma, hypertension and infections.

4.2.6. Statistical Analysis

In both studies, descriptive statistics were used to summarize the characteristics of the study population and to compare anti-infective use during pregnancy according to calendar year. Predictors for anti-infective drug use in the beginning of gestation were determined by means of a case-control analysis, using SAS Unconditional Logistic Regression program, adapted for the propose of Study 1. Cases were defined as pregnant women that filled at least one prescription for an anti-infective drug within the seven days before or after the first day of gestation. Annual trends in anti-infective drug use were analyzed using the Cochran-Armitage test for trend (Study 2).

All analyses were two-sided and $p \leq 0.05$ was considered significant. SAS 9.1 (SAS Institute Inc., Cary, NC, USA) was used to conduct analyses.

4.3. METHODS FOR STUDY 3 (EXPOSURE TO ANTI-INFECTIVE DRUGS DURING PREGNANCY AND THE RISK OF PRETERM BIRTH)

4.3.1. Study design

A case-control study was designed to determine whether there is an association between the use of anti-infective drugs during the last two trimesters of pregnancy and the risk of preterm birth. Three independent analyses were done: the first assessed the risk of preterm birth for all combined anti-infective drugs; the second assessed the risk for the classes of anti-infective drugs, and the third assessed the risk for individual types of anti-infective drugs.

4.3.2. Study population

Within the study population described in section 4.1.1, women meeting the following eligibility criteria were included in this study: (1) have between 15 and 45 years of age on the date of entry in the Registry defined as the first day of pregnancy; (2) to be continuously insured by the RAMQ drug plan for at least 12 months prior to the first day of gestation and during pregnancy; and (3) gave birth to a live born singleton. Given that multiple gestations are associated with an increased risk of maternal morbidity and mortality, independent of maternal age, we decided to select only singleton gestations [262]. The end of the pregnancy was defined as the calendar date of delivery. If a woman had more than one pregnancy between 1997 and 2003, the first pregnancy meeting eligibility criteria was considered for analysis.

4.3.3. Assessment of Exposure

In the three case-control analyses, exposure to anti-infective drugs was treated dichotomically. Exposure to at least one anti-infective drug and two or more anti-infectives were also assessed. Exposure time window was the pregnancy's second (>14 to ≤ 26 weeks of gestational age) or third trimester (>26 weeks until delivery). To be considered as exposed in a particular trimester, pregnant women had to have at least one prescription for an anti-infective drug in the corresponding trimester.

4.3.4. Assessment of Outcome

A case of preterm birth was defined as a delivery occurring before the 37^{th} week of gestation. Controls were defined as deliveries occurring ≥ 37^{th} week. The index date was the date of delivery and the unity of analysis was the pregnant woman. Gestational age was obtained from the Med-Echo files.

4.3.5. Covariates

The following variables were considered as potential confounders of the association between exposure and the risk of preterm birth, and were measured in the year before and during pregnancy: number of different types of medications used other than anti-infective, number of different prescribers for all medications, number of visits to the physician, visits to the emergency department and/or hospitalizations, diabetes (ICD-9 codes 250-259, 271.4, 790.2 and the filling of prescriptions for medications for diabetes), asthma (ICD-9 codes 493.0, 493.1, 493.9 and the filling of prescriptions for any anti-asthmatic drugs), hypertension (ICD-9 codes 640-642 and the filling of prescriptions for any antihypertensive drugs), infections (ICD-9 codes 001-136), respiratory tract infections (ICD-9 codes 460-466, 472-487), urinary

tract and sexually transmitted infections (ICD-9 codes 590, 599-599.6), diseases of the female genital tract (ICD-9 codes 617-619). We also determined the following socio-economic variables on the index date: maternal age, maternal place of residence, maternal RAMQ drug plan status, and calendar year of the pregnancy. Potential confounders were selected based in the available literature on the risk factors for the pregnancy outcomes of interest. In addition, a variable that modified the point estimate of the relationship between anti-infective exposure and adverse pregnancy outcome by more than 20% was considered a potential confounder, and was included in the multivariate model.

4.3.6. Statistical Analysis

Descriptive statistics, Student's t-tests, and chi-square tests were used to compare cases and controls. Univariate and multivariate unconditional logistic regression models were built, adjusting for important confounding factors and proxy variables for socio-economic, health service use, and co-morbidities. Consistency of the model was evaluated using the Hosmer–Lemeshow goodness-of-fit test. The association between anti-infective exposure and the risk of preterm birth was quantified by means of adjusted odds ratios (ORs), >eng</language></record></Cite></EndNote>[□□ HYPERLINK \l "_ENREF_62" \o "Pirotta, 2009 #86" □62]□□□. The current predic

4.4. METHODS FOR STUDY 4 (EXPOSURE TO ANTI-INFECTIVE DRUGS DURING PREGNANCY AND THE RISK OF SMALL-FOR-GESTATIONAL-AGE)

4.4.1. Study design

A case-control study was conducted to determine if there is an association between exposure to anti-infective drugs during the last two trimesters of pregnancy and the risk of SGA. Three independent analyses were done: the first analysis assessed the risk of SGA for all combined anti-infective drugs; the second assessed the risk of SGA for the classes of anti-infective drugs; and the third assessed the risk for individual types of anti-infective.

4.4.2. Study population

The same study population described on the section 4.3.2 was used for Study 4.

4.4.3. Assessment of Exposure

The same criteria for ascertainment of exposure described on the section 4.3.3 were used for Study 4.

4.4.4. Assessment of Outcome

A case of SGA was defined as a pregnancy resulting with a baby's weigh adjusted for gestational age and gender <10th percentile, according to the Canadian gender-specific reference curves [263]. A control was defined as a pregnancy resulting with a baby's weight adjusted for gestational age and

gender ≥10th percentile. The index date was defined as the date of delivery. Birth weight was obtained from Med-Echo and ISQ files.

4.4.5. Covariates

The following variables were considered as potential confounders of the association between exposure to anti-infective drugs and the risk of SGA, and were measured in the year before and during pregnancy: number of different types of medications used other than anti-infectives, number of different prescribers for all medications, number of visits to the physician, visits to the emergency department and/or hospitalizations, diabetes (ICD-9 codes 250-259, 271.4, 790.2 and the filling of at least one prescription for medications for diabetes, - AHFS codes 68:20.08, 68:20.20, 68:20.92), asthma (ICD-9 codes 493.0, 493.1, 493.9 and the filling of at least one prescription for any anti-asthmatic drugs), hypertension (ICD-9 codes 640-642 and the filling of at least one prescription for any antihypertensive drugs - AHFS class 24:08), infections (ICD-9 codes 001-136), respiratory tract infections (ICD-9 codes 460-466, 472-487), urinary tract and sexually transmitted infections (ICD-9 codes 590, 599-599.6), pelvic inflammatory disease (ICD-9 codes 614-616), pre-term rupture of membranes (ICD-9 codes 658), anemia (ICD-9 codes 280-285), periodontal disease (ICD-9 codes 521-525), renal disorders (ICD-9 codes 580-589), depression (ICD-9 codes 296, 309, 311), nutritional disorders (ICD-9 codes 260-269), and thyroid disorders (ICD-9 codes 240-246). In addition, we determined the following socio-economic variables at the index date from the RAMQ/ISQ databases: maternal age, maternal place of residence (urban versus rural), maternal RAMQ drug plan status (adherent versus welfare recipient) and calendar year of pregnancy.

4.4.6. Statistical Analysis

The same statistical tests described on the section 4.3.6 were used for Study 4.

4.5. METHODS FOR STUDY 5 (RISKS AND BENEFITS OF THE USE OF METRONIDAZOLE DURING PREGNANCY: A REVIEW OF THE EVIDENCE)

Study 5 is a systematic review of the evidence on the use of metronidazole during pregnancy. In order to retrieve studies addressing the issue, PubMed and EMBASE database were systematically searched to retrieve human studies published between 1964 through 2010. Combinations of the following MeSH terms were used: “metronidazole” or “prematurity” or “preterm birth” or “congenital malformations” or “birth defects” or “anomalies” or “pregnancy” as well as “antibiotics” or “bacterial vaginosis” or “tricomoniasis”. Additional references were identified from the reference lists of retrieved articles. All relevant articles, including prospective and retrospective studies, reviews and meta-analysis, published in English or French that examined the association between gestational exposure to metronidazole and the risk of adverse pregnancy outcomes (having data on preterm birth or birth defects) were reviewed. Only etiologic studies with clinical relevant definition of exposure were considered (exposure during the last two trimesters of pregnancy for studies evaluating prematurity and exposure during the first trimester for birth defects). Where the estimates for preterm birth or birth defects was not reported by authors, we calculated crude ORs and 95% confidence intervals (CI) from the available data in order to compare study results and interpret data. Analyses were performed using the SAS System for Windows Version 9.1.3 (SAS Institute Inc, North Carolina, USA).

Chapter 5
MANUSCRIPTS

The results of this thesis are presented in the following five manuscripts:

- **Prevalence and predictors of anti-infective use during pregnancy.** Fabiano SANTOS MSc, Driss ORAICHI PhD, Anick BÉRARD PhD. Pharmacoepidemiology and drug safety 2010; 19: 418–427.

- **Trends in anti-infective drugs use during pregnancy.** Fabiano SANTOS MSc, Odile SHEEHY MSc, Sylvie PERREAULT PhD, Ema FERREIRA PharmD, Anick BÉRARD Ph.D. Submitted to the Journal of Population Therapeutics and Clinical Pharmacology 2012.

- **Exposure to anti-infective drugs during pregnancy and the risk of preterm birth.** Fabiano SANTOS MSc, Odile SHEEHY MSc, Sylvie PERREAULT PhD, Ema FERREIRA PharmD, Anick BÉRARD Ph.D. Int J Antimicrob Agents. 2012 Feb;39(2):177-8.

- **Exposure to anti-infective drugs during pregnancy and the risk of small-for-gestationalage newborns: a case–control study.** Fabiano SANTOS MSc, Odile SHEEHY MSc, Sylvie PERREAULT PhD, Ema FERREIRA PharmD, Anick BÉRARD Ph.D. British Journal of Obstetritics and Gynaecology 2011 Oct;118(11):1374-82.

- **Risks and benefits of the use of metronidazole during pregnancy: a review of the evidence.** Fabiano SANTOS MSc, Ema FERREIRA PharmD, Anick BÉRARD Ph.D. Submitted to Drug Safety 2012.

Fabiano Santos conducted the studies, performed the analyses, and led the writing of the manuscripts. Sylvie Perreault and Ema Ferreira helped to interpret the results, and revised the manucripts for important intellectual content. Odile Sheehy and Driss Oraichid helped with the statistical methods and the interpretation of the results. Anick Berard conceived and supervised the studies. All authors read and approved the final version of the article.

5.1. PREVALENCE AND PREDICTORS OF ANTI-INFECTIVE USE DURING PREGNANCY

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5.1.1 ABSTRACT

Objectives: (1) Measure the prevalence and trends of anti-infective drug use before, during, and after pregnancy; (2) to list the doses, classes, types and indications for anti-infective use during pregnancy, and (3) to identify predictors associated with anti-infective drug use during pregnancy.

Methods: Retrospective cohort study within the Quebec Pregnancy Registry, which was created by the linkage of three administrative databases: RAMQ, Méd-Echo, and ISQ. Women were eligible if they were (1) continuously insured by the RAMQ drug plan for at least 12 months before the first day of gestation, during pregnancy and 12 months after the end of the pregnancy. 97680 pregnant women met the eligibility criteria. Data were collected for systemic agents. Logistic regression models were used to quantify predictors of use.

Results: Prevalence of anti-infective use during pregnancy was 24.5%. Penicillins use increased compared to others classes. The most frequent diagnosed infections were respiratory and urinary tract infections. Predictors associated with use at the beginning of gestation were having ≥ 2 different prescribers [OR= 3.83 (95% CI: 3.3-4.3)], diagnosis of urinary [OR= 1.50 (95% CI: 1.3-1.8)] and respiratory tract infection [OR= 1.40 (95% CI: 1.2-1.6)] in the year before pregnancy. Visits to an obstetrician/gynecologist were protective for use [OR= 0.81 (95% CI: 0.67-0.97)].

Conclusion: Anti-infective use during pregnancy is prevalent. The oldest and safest agents are preferred.

5.1.2. INTRODUCTION

Despite the fact that anti-infective drugs are among the most frequently used medications during pregnancy, there is still no agreement regarding the risks and benefits for the pregnant woman and the fetus (1). Thus far, only a few classes of antimicrobial compounds have been shown to be safe when used during gestation. Hence, essential anti-infective drugs used for the treatment of maternal infections are sometimes avoided, and this may contribute to the progression of intrauterine infections and their adverse consequences (2).

The prescription of an anti-infective drug for a given condition may change in response to the bacterial resistance profile. Therefore, pregnant women may be exposed to different anti-infective drugs/classes for the same infection, if the etiologic agent is resistant to the first therapy chosen (3). It is possible to describe a situation where a physician may be in the dilemma of prescribing a non-recommended drug, as a second choice, if the first recommended choice does not treat the infection. Nevertheless, the risk factors for use presented by the pregnant woman may be the same. In order to better address this issue, population-based data on the prevalence and trends of anti-infective drug use during pregnancy are needed. Identifying characteristics of anti-infective use during pregnancy will increase appropriate of use and therefore, improve mother's health (4,5).

Thus far, drug utilization reviews focusing specifically on anti-infective drug use during gestation have been scarce and were based on retrospective maternal recall of drug exposure (6-8). Given that a recent cross-sectional study conducted in a teratology information service in Canada showed that gestational exposure to antibiotics was the third most frequently inquired class of medication by health professionals, there is a need to better assess prevalence, trends and indication for their use during pregnancy (9).

Therefore, the objectives of this study were (I) to determine the prevalence and trends of anti-infective drug use before, during, and after pregnancy; [264] to list the doses, classes, types and indications for anti-infective use during pregnancy, and (III) to identify predictors associated with anti-infective drug use during pregnancy.

5.1.3. METHODS

5.1.3.1. Data sources

Data were obtained from the Quebec Pregnancy Registry, which contains data on all pregnancies occurring in Quebec between January 1st 1997 and December 31 2003. This registry was built from 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 Québec* (ISQ). The linkage between RAMQ and Med-Echo data was done using patients' *'Numéro d'assurance maladie'* [258], which is a unique identifier for all legal residents of Quebec. The mother-child linkage was possible using this unique identifier that links each baby born in Quebec to his/her mother in the RAMQ database. The linkage between the RAMQ and ISQ was done using the first name, family name and date of birth of both mother and child. The final Quebec Pregnancy Registry contains the following variables from each database:

1) The RAMQ database provides prospectively collected data on filled prescriptions, physician-based diagnoses (according to the International Classification of Diseases, ninth revision, ICD-9) (10), physician and emergency department visits, procedures and hospitalizations, health care providers and patient characteristics, and costs. The RAMQ covers costs of medical services for all Quebec residents and the RAMQ drug prescription

plan insures approximately 50% of all residents (11), which includes persons of 65 years or older, welfare recipients and their children, and all workers and their families who do not have access to a private drug insurance program. Pharmacists in Quebec are not allowed to substitute one drug for another different drug, even if the two drugs belong to same therapeutic class. However, pharmacists are given the privilege of substituting trademark drugs by their generic equivalent. It is estimated that 30% of women between 15 and 45 years of age in Quebec are covered by the RAMQ drug plan for their medications. Access to health care services between women covered for their medications by the RAMQ drug plan and those covered by private drug plan is similar (12).

2) The Med-Echo database provides acute care hospitalization data for all Quebec residents; it also records gestational age for planned abortions, miscarriages and deliveries. Gestational age is defined from the first day of the last menstrual period to the end of pregnancy, and confirmed by ultrasound around the 18th-20th week of gestation.

3) The ISQ provides demographic data on all births and deaths in Quebec. The ISQ contains demographic information on the mother (date of birth, age, marital status, mother-tongue, place of birth, area of residence, number of live births, number of deliveries), on the father (date of birth, age, mother-tongue, place of birth) and on the baby (gender, type of delivery, weight, gestational age, order in the family, date of birth).

Pregnancies are identifiable in the RAMQ database by a prenatal visit, an ICD-9 diagnostic code or a procedure code related to pregnancy such as an ultrasound or amniocentesis; and in the Med-Echo database by a procedure code related to pregnancy including a planned or spontaneous abortions or a delivery (liveborn or stillbirth). Given that the majority of pregnancies in

Quebec deliver in a hospital setting, and that all abortions (planned or spontaneous) are performed in subsidized clinics, we feel confident that we are capturing the great majority of all pregnancies. Only pregnancies that are not detected by the mother (before the pregnancy becomes diagnosed) are not captured in our registry.

Data recorded in the RAMQ, Med-Echo and ISQ database have been formally evaluated and found to be comprehensive and valid (13,14,15). RAMQ and Med-Echo databases have often been used in the past for epidemiological research leading to scientific articles published in peer-reviewed medical journals (16-18).

The final Quebec Pregnancy Registry has often been used to assess the risks and benefits of drug use during pregnancy (16,19, 20).

5.1.3.2. Study Population

Within the Registry, women meeting the following eligibility criteria were included in this study: they had to be (1) between 15 and 45 years of age on 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. The end of pregnancy was defined as the calendar date of a planned abortion, miscarriage, or delivery. If a woman had more than one pregnancy between 1998 and 2003, the first pregnancy meeting eligibility criteria was included for analysis.

5.1.3.3. Outcome measures

Anti-infective drugs were categorized using the 2008 Anatomical Therapeutic Chemical (ATC) classification index. Data were collected for oral systemic agents in the ATC subgroups J01 (antibacterial agents), J02 (antimycotics), and J04 (antimycobacterials). The ATC classification and guidelines are updated regularly and the system is widely used internationally for drug utilization studies (21).

The prevalence of anti-infective drug use during the 12 months before pregnancy was calculated by dividing the number of women receiving at least one prescription for an anti-infective in this 12-month period by the total number of women that met eligibility criteria. In addition, the prevalence of anti-infective drug use in the first trimester (≤14 weeks of gestational age), second trimester (>14 to ≤ 26 weeks of gestational age), and third trimester (>26 weeks of gestational age) of pregnancy was calculated by dividing the number of women filling at least one anti-infective prescription in the respective trimester by the number of women in the study during that time (depending on the outcome of the pregnancy - abortions, miscarriages or delivery - some women were counted in the denominator only in the first or second trimester). To be considered as exposed in a particular trimester, pregnant women had to have at least one prescription for an anti-infective drug in the corresponding trimester. For the five most frequently dispensed anti-infective in each period, the mean daily dosage and the mean duration of use were calculated.

Women were considered exposed on the first day of gestation and at the end of the second trimester of pregnancy if they filled a prescription for an anti-infective or if the duration of the prescription overlapped these periods. We allowed a 7-day grace period between consecutive prescriptions and thus,

women were considered exposed if the first day of gestation or the end of the second trimester of pregnancy fell during this grace period.

The following variables were considered as potential predictors of receiving at least one anti-infective drug at the beginning of gestation and were measured at this time: maternal age, maternal place of residence (urban versus rural), maternal RAMQ drug plan status (adherent versus welfare recipient), and calendar year of the pregnancy. The following variables were also considered as potential predictors of receiving at least one anti-infective drug at the beginning of gestation and were measured in the year before pregnancy: number of different types of medications used other than anti-infective, number of different prescribers for all medications, planned abortions or miscarriages, number of visits to the physician, visits to the emergency department and/or hospitalizations, diabetes, asthma, hypertension, infections, respiratory tract infections, human immunodeficiency virus (HIV) infection, gastro-intestinal infections, tuberculosis, urinary tract [7] and sexually transmitted infections (STI), fungal infections, parasitical infections, pelvic inflammatory disease (PID), and viral infections (Table 1).

The use of the data was approved by the CHU Sainte-Justine's ethics committee, and the '*Commission d'Accès à l'Information du Québec*' (CAI).

5.1.3.4. Statistical analysis

We chose to collect data on the first pregnancy meeting eligibility criteria to avoid having dependent units of analyses. Furthermore, the potential risk factors can change over time, conditional on the history of pregnancy.

Descriptive statistics were used to summarize the characteristic of the study population and to compare anti-invectives' users to non-users according to

trimester of exposure. Chi-square statistics and Student t-tests were used to compare proportions and means, respectively. Univariate and multivariate unconditional logistic regression models were built, adjusting for important confounders and proxy variables for socioeconomic, health services utilization and co-morbidities. A variable that modified the point estimate of the relationship between anti-infective exposure at the first day of gestational age and at the end of the second trimester by more than 20% was considered a predictor, and was included in the multivariate model. Consistency of the model was evaluated by Hosmer-Lemeshow goodness of fit test. Adjusted odds ratios (OR) along with 95% confidence intervals (95% CI) were estimated. All analyses were two-sided and $p \leq 0.05$ was considered significant. SAS version 8.2 (SAS Institute, Cary, NC) was used to conduct the analyses.

5.1.4. RESULTS

5.1.4.1. Study population, prevalence, indications for use and types of anti-infective used

A total of 97 680 pregnant women within the Quebec Pregnancy Registry met eligibility criteria and were thus, included in this study. The mean age of the cohort was 27.4 years, 35% of women were welfare recipients and 80% were living in an urban area on the beginning of gestation. The overall prevalence of anti-infective drug use during pregnancy was 24.5%. The prevalence of anti-infective drug use during the 12 months before gestation and during the 12 months after the end of pregnancy was 40.6% and 45.5%, respectively ($p < 0.01$, Table 2). Anti-infective drug use decreased during the first trimester compared to the year before pregnancy (15.3% versus 40.6%, $p < 0.01$) and continued to decrease during the second (10.0%) and third trimester (10.6%) (Table 2).

The most prevalent indications for anti-infective use are presented in Table 3. The most frequent indication for anti-infective use in all study periods in our cohort was respiratory tract infections with a peak of 65.7% of all indications for anti-infective use in the first trimester of pregnancy. PID was the second most diagnosed condition in all periods followed by UTI and STIs.

Table 4 lists the most prevalent anti-infective used stratified by ATC classes for each period. Penicillins use increased over time, whereas use of other anti-infective classes such as macrolides, quinolones, antimycotics, and sulfonamides decreased within the same period. Tetracycline was the least used class through all periods.

Amoxicillin was the most used individual drug in all periods, with highest frequency of use in the third trimester of pregnancy. Phenoxymethylpenicilline had an inversed time-trend tendency (highest prevalence in the first trimester and lowest prevalence in the third trimester). Two macrolides were among the most used drugs in all periods: clarithromycin before pregnancy and in the first trimester, and erythromycin in the second and in the third trimester.

Our data showed that ciprofloxacin was the fourth most frequently used anti-infective drug in the twelve months before pregnancy (7.4%) and in the first trimester (6.1%). Antimycotic drugs was the fourth most prevalent class of anti-infective used before (8.4%) and showed decreasing proportions of use during pregnancy.

5.1.4.2. Predictors of anti-infective use

Predictors of anti-infective drug use on the first day of gestation and at the end of the second trimester are summarized in Table 5 and Table 6, respectively. In multivariate analysis, predictors significantly associated with anti-infective drugs use at the beginning of gestation were being on welfare, having at least two different prescribers in the year before pregnancy, at least six visits to a physician in the year before pregnancy, having a diagnosis of infection, tuberculosis, UTI and STIs and respiratory tract infection in the year before pregnancy. Being on welfare on the last day of the second trimester and having at least six visits to a physician in the twelve months before pregnancy were associated with anti-infective use at the end of the second trimester of gestation. In contrast, having a visit to an obstetrician or gynecologist between the first day of gestation and the last day of the second trimester decreased the chance of taking an anti-infective drug at the end of the second trimester.

5.1.5. DISCUSSION

5.1.5.1. Trends and predictors of anti-infective drug use during pregnancy

To our knowledge, this is the first study that considers in an exhaustive way, the trends and predictors of anti-infective drugs use during pregnancy, and relevant clinical variables as predictors of use.

The frequency of anti-infective use during pregnancy in our cohort decreased progressively from the period before pregnancy through the end of pregnancy. The analysis was repeated for the nine months before and the nine months after the end of pregnancy, and results remained unchanged.

These findings may indicate that physicians are reluctant in prescribing anti-infective drugs once pregnancy is diagnosed. Studies about the utilization of anti-infective drugs during pregnancy in other countries show variable proportions of anti-infective drug use. In Hungary, a study showed that 17.0% of pregnant women were treated with antibiotics at some point during gestation (22). In Germany, 20.0% of pregnant women received antibiotics during pregnancy (1). In Denmark, 44.0% of pregnant women received prescriptions for at least one drug and the majority of prescriptions were for anti-infectives (28.7%) (23). High prevalence of anti-infective use in pregnancy was also reported in Australia (24) and in the USA (25, 26).

5.1.5.2. Indications for anti-infective use

In all study periods, respiratory tract infections were the most prevalent infections diagnosed in the cohort, followed by PID, UTI and STIs, gastrointestinal infections, fungal infections, parasitical infections and tuberculosis.

Acute respiratory infections are among the most frequent maternal infections during pregnancy, affecting about 10.0% of pregnant women (27). Our results may be viewed in light of what could be expected for a nordic country with long and rigorous winters. The physiological changes during pregnancy that makes pregnant women more susceptible to respiratory tract pathogens may also help explain this finding (28). In addition, pregnant women are often in contact with young children, so they are at greater risk of developing upper respiratory tract infections (29).

UTI and STIs are positively associated with a higher incidence of PID, which in turn is related to a increased risk for adverse pregnancy outcomes (30, 31). It was estimated that approximately 30-50% of PID diagnosed in Canada is

attributable to UTI and STIs (32). In our study, PID and UTI were the second and third most prevalent types of diagnosed infections during all periods, respectively. Our finding of a high prevalence of PID in third trimester of pregnancy is noteworthy. This may indicate that UTI and STIs diagnosed in the first and second trimester of pregnancy may be sub-optimally treated, and this would potentially be a risk factor for PID development in the third trimester.

5.1.5.3. Types of anti-infective drugs used

The most notable finding was the increasing frequency of penicillins use throughout all periods considered in our analysis. Other classes of anti-infective drugs like macrolides, quinolones, antimycotics and sulfonamides showed a contrary tendency with decreasing frequency of use. This analysis shows a shift in prescription to older anti-infective drugs once pregnancy is diagnosed. Similar trends were observed in others studies (1).

In our study, 66.0% of the anti-infective drugs used in the first trimester are considered safe – these drugs are not known to be associated with the risk of adverse pregnancy outcomes (4). This number rises to 77.0% in the second, and to 86.0% in the third trimester of pregnancy. This is a good indication that physicians are concerned in not to expose pregnant women to potentially harmful anti-infective drugs. However, the use of drugs of uncertain safety profiles such as ciprofloxacin and fluconazole in the first trimester, doxyciclyne in the second, and nitrofurantoin in the second and third trimesters, may also indicate the need for more studies on the risk-benefit ratio for the use of these drugs. The exposure to a potentially harmful anti-infective drug in the first trimester of gestation may be explained by the fact that 50.0% of all pregnancies in North America are unplanned (33). The pregnant woman and her doctor may not be aware of the existence of the

new fetus. The use of less secure and less effective anti-infectives once pregnancy is diagnosed may reflect an inappropriate prescribing practice among physicians.

5.1.5.4. Predictors for anti-infective use

Our results show that women who were welfare recipients at the beginning of gestation were slightly more at risk of use an anti-infective drug at the end of second trimester of pregnancy. Older pregnant women were less likely to use an anti-infective drug at the beginning of gestation than younger ones. This result is corroborated by the fact that infections in younger women are more prevalent (1).

Predictors related with a poor health status were among the factors associated with exposure of at least one anti-infective drug at the beginning of gestation and at the second trimester. These findings may indicate that the immune response before and during early pregnancy may play an important role in the likeliness of obtaining a prescription for an anti-infective drug during gestation. Several factors are responsible for a deficient immune response during early pregnancy (28,34,35) and it is important for physicians to be aware of underlying conditions that can lead to immunodeficiency states. Furthermore, having two or more prescribers in the year before pregnancy increased the risk of having a prescription for an anti-infective on the first day of gestation. This finding can be explained by the fact that the more physicians one consults, the more likely they are of receiving a prescription for a drug. The care management can be suboptimal when many physicians are consulted without prior knowledge on history of comorbidity and drug use. Visits to an obstetrician or gynecologist were protective for use of an anti-infective drug at the end of the second trimester. Pregnant women who visit their physicians may receive more appropriate treatment and

consequently, avoid conditions that predispose them to use of anti-infective drugs.

5.1.5.5. Strengths and limitations

This study was conducted on prospectively collected information obtained from administrative databases, and thus, we were able to assess a large number of potential variables and predictors related to anti-infective drug use during pregnancy. Nevertheless, this study has some limitations. The prevalence of anti-infective drug use was calculated on the basis of the drugs dispensed to study subjects and does not reflect the actual intake. On the other hand, the provincial drug plan requires that the beneficiary pay a portion of the costs of the prescription medications. This increases the likelihood that prescriptions that are filled are in fact consumed. We did not address appropriateness of anti-infective prescriptions according to the patterns of the most prevalent infections for each period, and we did not evaluate the switches between classes according to infections because we do not have data on the specific bacterial agent related to the infection.

Furthermore, multiple testing could explain in part some of our findings. Data were not available for pregnant women who are not covered by the RAMQ drug plan for their medications, nor on anti-infective use for more severe infections in hospital setting. This will likely underestimate the prevalence of anti-infective use for certain classes of drugs. Given the free universal healthcare system in Quebec, we do not believe that this would confound our results. Indeed, Bérard and Lacasse have shown that this could affect the generalizability of some findings that are more strongly associated with socio-demographic factors, but this will not affect internal validity (12).

5.1.6. CONCLUSION

The use of anti-infective drugs during pregnancy is prevalent and prescribers seem to be concerned about the choice of older and well-known safety-profile anti-infective drugs. However, the use of potentially harmful anti-infectives in critical periods raises the question of whether the anti-infective prescribing practice and use are really appropriate. Health care professionals must consider the risk profiles of anti-infective agents in making prescribing decisions during pregnancy. Predictors related with lower social/health status before and during the first two trimesters of pregnancy increased the likelihood of using at least one anti-infective drug.

We highlight the need for evidence-based studies that evaluate the risks and benefits of anti-infective drug use during pregnancy adjusting for indication for use.

5.1.7. REFERENCES

1. Amann U, Egen-Lappe V, Strunz-Lehner C, Hasford J. Antibiotics in pregnancy: analysis of potential risks and determinants in a large German statutory sickness fund population. Pharmacoepidemiol.Drug Saf 2006;15:327-37.

2. Dashe JS, Gilstrap LC, III. Antibiotic use in pregnancy. Obstet.Gynecol.Clin.North Am. 1997;24:617-29.

3. Guidelines. Antimicrobial Therapy - A Concise Canadian Guide 2007. Montreal: Prism, 2007.

4. Norwitz ER, Greenberg JA. Antibiotics in pregnancy: are they safe? Rev.Obstet.Gynecol. 2009;2:135-36.

5. Sa del FF, Gerenutti M, Groppo FC. Antibiotics and pregnancy. Pharmazie 2005;60:483-93.

6. Loebstein R, Addis A, Ho E, Andreou R, Sage S, Donnenfeld AE et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. Antimicrob.Agents Chemother. 1998;42:1336-39.

7. Bar-Oz B, av-Citrin O, Shechtman S, Tellem R, Arnon J, Francetic I et al. Pregnancy outcome after gestational exposure to the new macrolides: A prospective multi-center observational study. Eur.J.Obstet.Gynecol.Reprod.Biol. 2008;141:31-34.

8. Sarkar M, Woodland C, Koren G, Einarson AR. Pregnancy outcome following gestational exposure to azithromycin. BMC.Pregnancy.Childbirth. 2006;6:18.

9. Gendron MP, Martin B, Oraichi D, Berard A. Health care providers' requests to Teratogen Information Services on medication use during pregnancy and lactation. Eur.J Clin.Pharmacol. 2009.

10. World Health Organization. International Classification of Diseases. 1997.

11. Régie de l'assurance maladie du Québec: Statistiques annuelles. Goverment of Quebec. 1997.

12. Berard, A. Lacasse A. Validity of perinatal pharmacoepidemiologic studies using data from the RAMQ administrative database. Can J Clin Pharmacol. 2009;16(2):e360-9.

13. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. J.Clin.Epidemiol. 1995;48:999-1009.

14. Vilain A, Otis S, Forget A, Blais L. Agreement between administrative databases and medical charts for pregnancy-related variables among asthmatic women. Pharmacoepidemiol.Drug Saf 2008;17:345-53.

15. Levy AR, Mayo NE, Grimard G. Rates of transcervical and pertrochanteric hip fractures in the province of Quebec, Canada, 1981-1992. Am.J Epidemiol. 1995;142:428-36.

16. Blais L, Desgagne A, LeLorier J. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and the risk of cancer: a nested case-control study. Arch.Intern.Med. 2000;160:2363-68.

17. Garbe E, LeLorier J, Boivin JF, Suissa S. Risk of ocular hypertension or open-angle glaucoma in elderly patients on oral glucocorticoids. Lancet 1997;350:979-82.

18. Avorn J, Monette J, Lacour A, Bohn RL, Monane M, Mogun H et al. Persistence of use of lipid-lowering medications: a cross-national study. JAMA 1998;279:1458-62.

19. Ramos E, Oraichi D, Rey E, Blais L, Berard A. Prevalence and predictors of antidepressant use in a cohort of pregnant women. BJOG. 2007;114:1055-64.

20. Berard A, Azoulay L, Koren G, Blais L, Perreault S, Oraichi D. Isotretinoin, pregnancies, abortions and birth defects: a population-based perspective. Br.J.Clin.Pharmacol. 2007;63:196-205.

21. WHO Collaborating Centre for Drug Statistics Methodology. WHO Collaborating Centre for Drug Statistics Methodology. http://www.whocc.no/atcddd/ (accessed 5 December 2008).

22. Czeizel AE, Rockenbauer M, Olsen J. Use of antibiotics during pregnancy. Eur.J.Obstet.Gynecol.Reprod.Biol. 1998;81:1-8.

23. Olesen C, Steffensen FH, Nielsen GL, de Jong-van den Berg, Olsen J, Sorensen HT. Drug use in first pregnancy and lactation: a population-based

survey among Danish women. The EUROMAP group. Eur.J.Clin.Pharmacol. 1999;55:139-44.

24. Henry A, Crowther C. Patterns of medication use during and prior to pregnancy: the MAP study. Aust.N.Z.J.Obstet.Gynaecol. 2000;40:165-72.

25. Splinter MY, Sagraves R, Nightengale B, Rayburn WF. Prenatal use of medications by women giving birth at a university hospital. South.Med.J. 1997;90:498-502.

26. Chamany S, Schulkin J, Rose CE, Jr., Riley LE, Besser RE. Knowledge, attitudes, and reported practices among obstetrician-gynecologists in the USA regarding antibiotic prescribing for upper respiratory tract infections. Infect.Dis.Obstet.Gynecol. 2005;13:17-24.

27. Schanzer DL, Langley JM, Tam TW. Influenza-attributed hospitalization rates among pregnant women in Canada 1994-2000. J.Obstet.Gynaecol.Can. 2007;29:622-29.

28. Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. Emerg.Infect.Dis. 2006;12:1638-43.
29. Wise R. Prescribing in Pregnancy. British Medical Journal 1987.

30. Macejko AM, Schaeffer AJ. Asymptomatic bacteriuria and symptomatic urinary tract infections during pregnancy. Urol.Clin.North Am. 2007;34:35-42.

31. Andriole VT, Patterson TF. Epidemiology, natural history, and management of urinary tract infections in pregnancy. Med.Clin.North Am. 1991;75:359-73.

32. Sexually Transmitted Diseases in Canada: 1996 Surveillance Report . Health Canada . Government of Canada, 1997.

33. Koren G, MacLeod S, Davis D. Drugs in pregnancy: acknowledging challenges--finding solutions. Can.J.Clin.Pharmacol. 2007;14:e2-e4.

34. Zenclussen AC, Schumacher A, Zenclussen ML, Wafula P, Volk HD. Immunology of pregnancy: cellular mechanisms allowing fetal survival within the maternal uterus. Expert.Rev.Mol.Med. 2007;9:1-14.

35. Le BP, Tabiasco J. [Immunology of pregnancy: renewed interest]. Med.Sci.(Paris) 2006;22:745-50.

Table 1. Type of infections, comorbidities and ICD-9/AHFS assessment code.

Type of infection	ICD-9 and AHFS code
Diabetes	ICD-9 codes 250-259, 271.4, 790.2 and the filling of prescriptions for medications for diabetes, - American Hospital Formulary Service (AHFS) 68:20.08, 68:20.20, 68:20.92
Asthma	ICD-9 codes 493.0, 493.1, 493.9 and the filling of prescriptions for any anti-asthmatic drugs
Hypertension	ICD-9 codes 640-642 and the filling of prescriptions for any antihypertensive drugs - AHFS class 24:08
Infections	ICD-9 codes 001-136
Respiratory tract infections	ICD-9 codes 460-466, 472-487
HIV infection	ICD-9 codes 042-044
Gastro-intestinal infections	ICD-9 codes 001-009),
Tuberculosis	ICD-9 codes 010-018
UT/STI	ICD-9 codes 590, 599-599.6
Fungal infections	ICD-9 codes 110-118
Parasitical infections	ICD-9 codes 120-136
PID	ICD-9 codes 614-616
Viral infections	ICD9 codes 045-066

Table 2. Prevalence of anti-infective drug use before, during, and after pregnancy.

Period	Number of anti-infective drug users	Total number of women*	Percentage (95% Confidence interval - CI)
During the 12 months before pregnancy	39724	97680	40.6 (40.3 – 40.9)
During pregnancy	23913	97680	24.5 (24.2 – 24.7)
During the first trimester of pregnancy (≤14 weeks of gestational age)	14990	97680	15.3 (15.1 – 15.5)
During the second trimester of pregnancy (>14 to ≤ 26 weeks of gestational age)	8074	80164	10.0 (9.8 – 10.2)
During the third trimester of pregnancy (>26 weeks of gestational age)	6005	56578	10.6 (10.3 – 10.8)
During the 12 months after the end of pregnancy**	44499	97680	45.5 (45.2 – 45.8)

*Depending on the pregnancy outcome (abortion, miscarriage or delivery), some women were not included in the denominators for the prevalence of use in the second or third trimester;

**The end of pregnancy was defined as a planned abortion, a miscarriage, or a delivery, whichever occurred.

Table 3. Most prevalent diagnosed infections treated with anti-infectives, before, during and after pregnancy.

Type of infection, n (%)*	**During the 12 months before gestation (n=97680)****	**During the first trimester of pregnancy (≤14 weeks of gestational age) (n=97680)****	**During the second trimester of pregnancy (>14 to ≤ 26 weeks of gestational age) (n=80164)****	**During the third trimester of pregnancy (>26 weeks of gestational age) (n=56578)****	**During the 12 months after the end of the pregnancy** (n=97680)****
Respiratory tract infections	52708 (62.0)	12255 (65.7)	5640 (63.5)	4514 (42.2)	45284 (57.5)
Pelvic Inflammatory disease	16420 (19.3)	3873 (20.7)	1318 (14.8)	2611 (24.4)	17606 (22.4)
Urinary tract and sexually transmitted	8128 (9.5)	659 (3.5)	852 (9.6)	783 (7.3)	7133 (9.0)
Gastro-intestinal infections	2113 (2.5)	680 (3.6)	336 (3.8)	302 (2.8)	2133 (2.7)
Fungal infections	1733 (2.0)	350 (1.9)	153 (1.7)	193 (1.8)	2027 (2.5)
Parasitical Infections	1153 (1.3)	252 (1.3)	169 (1.9)	150 (1.4)	1199 (1.5)
Tuberculosis	670 (0.8)	97 (0.5)	94 (1.0)	52 (0.4)	738 (0.9)
Others	2066 (2.4)	466 (2.5)	312 (3.5)	2093 (19.5)	2595 (3.3)
Total of Infections	84991 (100.0)	18632 (100.0)	8874 (100.0)	10689 (100.0)	78715 (100.0)

* Number and percent of all infections during each period

**Number of women included in the analysis in each period. Depending on the pregnancy outcome (abortion, miscarriage or delivery), some women were not included in the denominators for the prevalence of use in the second or third trimester.

Table 4. Prevalence of anti-infective use before pregnancy, during the first, second and third trimester, stratified by drug class.

Class of Anti-infectives (Percentages may not add up to 100% due to rounding. Groups are not mutually exclusive since a woman could have received more than one class of anti-infective. * Were excluded for this analyses the ATC/WHO subgroups J05 (antivirals for systemic use), J06 (immune sera and immunoglobulins) and J07 (vaccines). ** Number of women who received at least one antibiotic during the first, second, or third trimester, respectively.	**Number of prescriptions and percent** **12 months before pregnancy (n=39724)****	**Number of prescriptions and percent** **First trimester** (≤14 weeks of gestational age) **(n=14990)****	**Number of prescriptions and percent** **Second trimester** (>14 to ≤ 26 weeks of gestational age) **(n=8074)****	**Number of prescriptions and percent** **Third trimester** (>26 weeks of gestational age) **(n=6005)****
Penicillins	23481 (37.7)	7306 (40.8)	4971 (54.3)	4255 (62.0)
Macrolides, lincosamides and streptogramins	12706 (20.4)	3519 (19.6)	1518 (16.6)	1097 (16.0)
Quinolones	5881 (9.4)	1396 (7.8)	183(2.0)	59 (0.8)
Antifongiques	5257 (8.4)	1217 (6.8)	192 (2.1)	110 (1.6)
Sulfonamides	3980 (6.4)	860 (4.8)	202 (2.2)	82 (1.2)
Cephalosporins	3927 (6.3)	1074 (6.0)	622 (6.8)	600 (8.7)
Others antibacterials	3304 (5.3)	1253 (7.0)	933 (10.2)	603 (8.8)
Tetracyclines	3117 (5.0)	1110 (6.2)	490 (5.3)	21 (0.3)
Others	685 (1.1)	165 (0.9)	36 (0.4)	27 (0.4)
Total	62338 (100.0)	17901 (100.0)	9147 (100.0)	6854 (100.0)

Table 5. Predictors of anti-infective drug use at the beginning of gestation

	Users on the first day of gestation (n=1840)	Non-users on the first day of gestation (n=95 840)	Crude OR (95% CI)	Adjusted OR* (95% CI)
On the first day of gestation				
Maternal age, years (mean, SD)	26.7 (6.1)	27.4 (6.1)	0.98 (0.97-0.98)	0.98 (0.98-0.99)
Urban living, n (%)				
No	355 (19.3)	19248 (20.0)	1.00	1.00
Yes	1485 (80.7)	76592 (80.0)	1.05 (0.93-1.18)	1.00 (0.90-1.13)
Welfare recipient, n (%)				
No	1065 (57.8)	60279 (65.2)	1.00	1.00
Yes	775 (42.1)	32233 (34.8)	1.36 (1.24-1.50)	1.12 (1.02-1.24)
During the 12 months before the first day of gestation				
Number of different prescribers, n (%)				
1	283 (15.4)	50083 (52.2)	1.00	1.00
≥ 2	1557 (84.6)	45757 (47.7)	6.02 (5.30-6.80)	3.83 (3.30-4.30)
Number of different medications used other than anti-infectives, n (%)				
0-2	927 (50.4)	69581 (72.6)	1.00	1.00
3-5	556 (30.2)	19648 (20.5)	2.12 (1.91-2.36)	0.87 (0.78-1.0)
≥ 6	357 (19.4)	6611 (6.9)	4.05 (3.57-4.60)	1.37 (1.18-1.50)

Number of visits to a physician, n (%)				
0-2	228 (12.4)	30783 (32.1)	1.00	1.00
3-5	394 (21.4)	23245 (24.2)	2.28 (1.95-2.70)	1.26 (1.06-1.50)
≥ 6	1218 (66.2)	41812 (43.6)	3.94 (3.14-4.53)	1.37 (1.161.62)
Emergency department visit/hospitalization n (%)				
No	1494 (81.2)	81785 (85.3)	1.00	1.00
Yes	346 (18.8)	14055 (14.7)	1.35 (1.19-1.51)	0.9 (0.80-1.0)
Diabetes, n (%)				
No	1805 (98.1)	94845 (98.9)	1.00	1.00
Yes	35 (1.9)	995 (1.1)	1.85 (1.31-2.6)	1.00 (0.7-1.5)
Hypertension, n (%)				
No	1808 (98.3)	94680 (98.8)	1.00	1.00
Yes	32 (1.7)	1160 (1.2)	1.45 (1.00-2.00)	0.86 (0.60-1.20)
Asthma, n (%)				
No	1433 (77.9)	83493 (87.2)	1.00	1.00
Yes	407 (22.1)	12347 (12.8)	1.92 (1.71-2.14)	1.13 (1.00-1.20)

Infections, n (%)				
No	518 (28.15)	53520 (55.84)	1.00	1.00
Yes	1,322 (71.8)	42320 (44.2)	3.20 (2.91-3.50)	1.30 (1.11-1.50)
HIV, n (%)				
No	1837 (99.84)	95803 (99.96)	1.00	1.00
Yes	3 (0.16)	37 (0.04)	4.30 (1.3-13.7)	2.00 (0.61-6.00)
Gastro intestinal infections, n (%)				
No	1801 (97.8)	94547 (98.65)	1.00	1.00
Yes	39 (2.1)	1293 (1.35)	1.60 (1.15 – 2.18)	0.90 (0.60-1.23)
Tuberculosis, n (%)				
No	1817 (98.75)	95654 (99.8)	1.00	1.00
Yes	23 (1.25)	186 (0.2)	6.50 (4.20 – 10.0)	4.50 (2.80-7.10)
Urinary tract and sexually transmitted infections, n (%)				
No	1627 (88.4)	91221 (95.2)	1.00	1.00
Yes	213 (11.6)	4619 (4.8)	2.60 (2.20 – 2.90)	1.5 (1.30-1.81)
Fungal infection, n (%)				
No	1759 (95.6)	93961 (98.04)	1.00	1.00

Yes	81 (4.4)	1879 (1.96)	2.30 (1.80 – 2.90)	1.30 (1.01-1.80)
Parasitical infection, n (%)				
No	1803 (97.9)	94886 (99.0)	1.00	1.00
Yes	37 (2)	954 (1)	2.00 (1.50-2.80)	1.10 (0.70-1.50)
Viral infection, n (%)				
No	1670 (90.8)	90242 (94.1)	1.00	1.00
Yes	170 (9.2)	5598 (5.84)	1.65 (1.40-1.92)	1.04 (0.87-1.22)
Respiratory tract infection, n (%)				
No	849 (46.2)	66649 (69.6)	1.00	1.00
Yes	991 (53.8)	29191 (30.4)	2.60 (2.40 – 2.92)	1.40 (1.20-1.60)
Pelvic inflammatory disease, n (%)				
No	1495 (81.2)	85766 (89.5)	1.00	1.00
Yes	345 (18.7)	10074 (10.5)	1.90 (1.70-2.20)	1.14 (1.00-1.30)

Percentages may not add up to 100% due to rounding.

*Adjusted for the covariates in the table and calendar year of pregnancy.

Table 6. Predictors of anti-infective drug use at the end of the second trimester

Predictor	Users on the last day of second trimester of gestation (n= 685)	Non-users on last day of second trimester of gestation (n=55956)	Crude OR (95% CI)	Adjusted OR* (95% CI)
At the end of the second trimester of gestation				
Maternal age, years (mean, standard deviation)	26.7 (5.5)	27.4 (5.6)	0.97 (0.96-0.98)	0.99 (0.97-1.0)
Urban inhabitants, n (%)				
No	170 (24.8)	13117 (23.5)	1.00	1.00
Yes	515 (75.2)	42839 (76.5)	0.92 (0.8-1.1)	0.86 (0.7-1.0)
Welfare, n (%)				
No	387 (56.5)	36576 (67.9)	1.00	1.00
Yes	298 (43.5)	17268 (32.1)	1.63 (1.4-1.9)	1.21 (1.03-1.4)
During the 12 months before the first day of gestation				
Number of visits to a physician, n (%)				
0-2	136 (19.8)	18200 (32.5)	1.00	1.00
3-5	138 (20.15)	13587 (24.2)	1.36 (1.07-1.72)	0.98 (0.76-.26)
≥ 6	411 (60.0)	24169 (43.1)	2.27 (1.87-2.7)	1.00 (0.78-1.2)
Diagnosis of infections,n (%)				
No	275 (40.2)	31719 (56.7)	1.00	1.00
Yes	410 (59.8)	24237 (43.3)	1.90 (1.7-2.2)	1.32 (1-1.8)

Continuation of Table 6

Between the first day of gestation and the end of second trimester of gestation

Number of different prescribers, n(%)				
1	236 (34.4)	43301 (77.4)	1.00	1.00
≥ 2	449 (65.5)	12655 (22.6)	6.51 (5.55-7.63)	4.25 (3.5-5.1)
Asthma, n (%)				
No	549 (80.1)	52033 (92.9)	1.00	1.00
Yes	136 (20.0)	3923 (7.0)	3.30 (2.7-4.00)	1.68 (1.3-2.01)
Infections, n (%)				
No	312 (45.5)	43086 (77.0)	1.00	1.00
Yes	373 (54.4)	12870 (23.0)	4.01 (3.4-4.6)	1.43 (1.00-2.00)
Respiratory tract infection, n (%)				
No	391 (57.0)	47574 (85.0)	1.00	1.00
Yes	294 (43.0)	8382 (15.0)	4.26 (3.6-5)	1.95 (1.41-2.7)
Visit to an Obstetrician or Gynecologist, n (%)				
No	163 (23.2)	12174 (21.8)	1.00	1.00
Yes	522 (76.2)	43782 (78.2)	0.90 (0.75-1.06)	0.81 (0.67-0.97)

Percentages may not add up to 100% due to rounding.

*Adjusted for the covariates in the table, table 5 and calendar year of the pregnancy.

5.2. TRENDS IN ANTI-INFECTIVE DRUGS USE DURING PREGNANCY – A SHORT COMMUNICATION

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5.2.1. ABSTRACT

Background: Development of knowledge in understanding the use of antibiotics during pregnancy has been limited by difficulties in testing medications in pregnant women and lack of good evidence-based data. Overuse of broad spectra antibiotics 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 anti-infective use 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 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-base studies on prescription’s trends during pregnancy.

5.2.2. INTRODUCTION

Physicians and health care providers face on a daily basis the question of whether to prescribe or not anti-infective drugs to pregnant women. Healthy pregnant women are no more susceptible to most infections than their non-pregnant counterparts. However, when an infection occurs during pregnancy, it can be associated with obstetric complications, and physicians can be reluctant to prescribe anti-infectives since some antibiotics (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 antibiotics 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 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 antibiotics in an effort to decrease resistance (4). However, the development of knowledge in understanding the use of broad spectrum antibiotics 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). Use and overuse of broad spectra antibiotics 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.

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.

5.2.3. METHODS

5.2.3.1. Data sources

The study was conducted using the Quebec Pregnancy Registry, which contains data on all pregnancies with drug plan coverage occurring in Quebec between January 1st 1998 and December 31 2002. This registry was built from 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 Québec* (ISQ). The final Quebec Pregnancy Registry contains the following variables from each database:

1) The RAMQ database provides prospectively collected data on filled prescriptions, physician-based diagnoses (according to the International Classification of Diseases, ninth revision, ICD-9) (6), physician and emergency department visits, procedures and hospitalizations, health care providers and patient characteristics. The RAMQ covers costs of medical services for all Quebec residents and the RAMQ drug prescription plan insures approximately 50% of all residents, which includes persons of 65 years or older, welfare recipients and their children, and all workers and their families who do not have access to a private drug insurance program (7). The maternal use of prescribed anti-infective drugs was identified from the RAMQ pharmacy files.

2) The Med-Echo database provides acute care hospitalization data for all Quebec residents; it also records gestational age for planned abortions, miscarriages and deliveries.

3) The ISQ provides demographic data on all births and deaths in Quebec.

In order to form the Registry, the linkage between RAMQ and Med-Echo was done using patients' *Numéro d'assurance maladie* [258], which is a unique identifier for all legal residents of Quebec. The mother-child linkage was possible using the unique identifier that links each baby born in Quebec to his/her mother in the RAMQ database. The linkage between the RAMQ and ISQ was done using the first name, family name and date of birth of both the mother and child. Pregnancies are identifiable in the RAMQ database by a prenatal visit, an ICD-9 diagnostic code or a procedure code related to pregnancy such as an ultrasound or amniocentesis. MedEcho database furnish procedure codes related to pregnancy, including a planned or spontaneous abortions or deliveries (live births or stillbirth).

Data recorded in the RAMQ, Med-Echo and ISQ database have been formally evaluated and found to be comprehensive and valid (8). RAMQ and Med-Echo databases have often been used in the past for epidemiological research leading to scientific articles published in peer-reviewed medical journals (9). The final Quebec Pregnancy Registry has often been used to assess the risks and benefits of drug use during pregnancy (10). The used 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).

5.2.3.2. Study Population

Anti-infective use was analysed for pregnant women meeting the following criteria: (1) have between 15 and 45 years of age on 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.

5.2.3.3. Trends in anti-infective drugs use

We analysed trends for new prescriptions of oral systemic anti-infectives 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).

5.2.3.4. 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 giving 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.

5.2.4. RESULTS

97 680 pregnant women within the Quebec Pregnancy Registry met eligibility criteria and were included in the study. From this total, 23913 (24.5%) were exposed at least once to an anti-infective. There were 34753 filled prescriptions for anti-infective drugs during the five-year period considered: 33510 were new filled prescriptions (3.57% were refill prescriptions).

The overall use of anti-infective drugs during pregnancy decreased from 1998 to 2002 ($p \leq 0.05$ for trends, 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 10.16% in 2002. Drugs like amoxicillin, erythromycin, doxycyclin and SXT showed decrease in their use during the same period. These results and the effectives for each year are summarized in Table 1.

5.2.5. DISCUSSION

The gradual decrease in the use of anti-infective drugs (all confounded) 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 is preferred over those with a broad spectrum for the treatment of well-established infection. Studies about the use of broad-spectrum anti-infectives in other clinical contexts showed increased trends in prescription (11). Prevalence of use of these drugs during pregnancy in other countries varies (12).

Several recent studies were published reporting an increased risk of congenital malformations after exposure to SXT (13). Even if this drug is prescribed for infectious diseases of the urinary, respiratory, and gastrointestinal tract, the impact of these studies may have caused physicians to decrease prescription of this drug during pregnancy, as observed in our cohort. 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 that 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 efficacy14. However, increasing nitrofurantoin resistance complicates 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 antibiotic 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 (13). We believe that, in our study, women were exposed to this drug in the first trimester of pregnancy, before being aware of their condition. 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). This fact may also be responsible for the augmentation of the use of doxycycline and fluconazole. Furthermore, oral fluconzaole became more popular than topical azoles for treatment of vaginal candidiasis (13). 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 (15).

Finally, we observed that macrolides showed increase 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 once daily 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 when administered as a single one-gram dose. The single oral dose administration increases compliance when compared to the standard erythromycin or amoxicillin 7-day regimen (16). 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. Again, prescription practice seems to be related to the evidence of safety and efficacy of medications during pregnancy. Nevertheless, there is controversy on diagnosis of pregnancy infections in the absence of bacterial culture data;

emergency physicians are usually required to choose empiric therapy without such information (17).

This study was conducted on prospectively collected information 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 pay a portion of the costs of the prescription medications. This increases the likelihood that prescriptions that are filled are in fact consumed.

5.2.6. CONCLUSION

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-base studies on prescription’s trends during pregnancy.

5.2.7. REFERENCES

1. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. N Engl J Med 1998; 338:1128-37.

2. Bruel H, Guillemant V, Saladin-Thiron C, Chabrolle JP, Lahary A, Poinsot J. Hemolytic anemia in a newborn after maternal treatment with nitrofurantoin at the end of pregnancy. Arch Pediatr 2000; 7:745-47.

3. Lockitch G. Maternal-fetal risk assessment. Clin Biochem 2004; 37:447-49.

4. Conly JM, McEwen S, Hutchinson J, Boyd N, Callery S, Bryce E. Canadian Committee on Antibiotic Resistance report. Can J Infect Dis Med Microbiol 2004; 5:257-60.

5. Vallano A, Arnau JM. Antimicrobials and pregnancy. Enferm Infecc Microbiol Clin 2009; 27:536-42.

6. International Classification of Diseases. 1997.

7. Régie de l'assurance maladie du Québec: Statistiques annuelles. 1997.

8. Berard A, Lacasse A. Validity of perinatal pharmacoepidemiologic studies using data from the RAMQ administrative database. Can J Clin Pharmacol 2009; 16:e360-e369.

9. Vilain A, Otis S, Forget A, Blais L. Agreement between administrative databases and medical charts for pregnancy-related variables among asthmatic women. Pharmacoepidemiol Drug Saf 2008; 17:345-53.

10. Berard A, Azoulay L, Koren G, Blais L, Perreault S, Oraichi D. Isotretinoin, pregnancies, abortions and birth defects: a population-based perspective. Br J Clin Pharmacol 2007; 63:196-205.

11. Roumie CL, Halasa NB, Grijalva CG, Edwards KM, Zhu Y, Dittus RS et al. Trends in antibiotic prescribing for adults in the United States--1995 to 2002. J Gen Intern Med 2005; 20:697-702.

12. Santos F, Oraichi D, Berard A. Prevalence and predictors of anti-infective use during pregnancy. Pharmacoepidemiol Drug Saf 2010; 19:418-27.

13. Guidelines. Antimicrobial Therapy - A Concise Canadian Guide 2007. Montreal: Prism, 2007.

14. Smaill F, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. Cochrane Database Syst Rev 2007; CD000490.

15. Public Health Agency of Canada. Canadian Perinatal Health Report 2008. 2008. Ottawa, Ministry of Health.

16. Pitsouni E, Iavazzo C, Athanasiou S, Falagas ME. Single-dose azithromycin versus erythromycin or amoxicillin for Chlamydia trachomatis infection during pregnancy: a meta-analysis of randomised controlled trials. Int J Antimicrob Agents 2007; 30:213-21.

17. Norwitz ER, Greenberg JA. Antibiotics in pregnancy: are they safe? Rev Obstet Gynecol 2009; 2:135-36.

Table 1. Trends in anti-infective drug use during pregnancy

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*							
Yes	6436 (25.0%)	5524 (24.4%)	4794 (25.1%)	4171 (24.0%)	2988 (23.1%)	23913 (24.4%)	0.0002 – decrease
No	19269 (74.9%)	17093 (75.8%)	14299 (74.8%)	13167 (75.9%)	9939 (76.9%)	73767 (75.5%)	
						97680 (100%)	
Prescriptions filled for anti-infectives*							
New prescriptions	9062 (97.2%)	7758 (96.5%)	6770 (96.9%)	5788 (95.0%)	4132 (95.4%)	33510 (96.4%)	
Refill prescriptions	254 (2.7%)	280 (3.4%)	214 (3.0%)	299 (4.9%)	196 (4.5%)	1243 (3.7%)	
Spectrum of Anti-infective drug used**							
Broad spectrum	3529 (38.9%)	2726 (35.1%)	2075 (30.6%)	1679 (29.0%)	1137 (24.5%)	11146 (33.2%)	<.0001 - decrease
Narrow spectrum	5533 (61.0%)	5032 (64.8%)	4695 (69.3%)	4109 (70.9%)	2995 (72.4%)	22364 (66.7%)	
						33510 (100%)	

Classes of anti-infective drugs used**

Penicillins	4980 (54.9%)	4132 (53.2%)	3154 (46.5%)	2553 (44.1%)	1712 (41.4%)	16531 (49.3%)	<.0001 – decrease
Macrolides	1362 (15.0%)	1129 (14.5%)	1209 (17.8%)	1152 (19.9%)	814 (19.7%)	5666 (16.9%)	<.0001 - increase
Quinolones	305 (3.3%)	348 (4.4%)	359 (5.3%)	337 (5.8%)	293 (7.0%)	1642 (4.9%)	<.0001 - increase
Cephalos-porins	437 (4.8%)	399 (5.1%)	348 (5.1%)	258 (4.4%)	172 (4.1%)	1614 (4.8%)	0.0579
Tetracyclines	294 (3.2%)	256 (3.3%)	288 (4.2%)	402 (6.9%)	275 (6.6%)	1515 (4.5%)	<.0001 - increase
UTI	341 (3.76 %)	308 (3.7%)	312 (4.6%)	301 (5.2%)	218 (5.2%)	1480 (4.4%)	<.0001 - increase
Antimycotics	307 (3.3%)	298 (3.8%)	293 (4.3%)	244 (4.2%)	208 (5.0%)	1350 (4.0%)	<.0001 - increase
Anti-protozoals	342 (3.7%)	289 (3.7%)	273 (4.0%)	121 (2.0%)	208 (5.0%)	1233 (3.6%)	0.9878
Others	270 (2.9%)	252 (3.2%)	271 (4.0%)	239 (4.1%)	135 (3.2%)	1167 (3.4%)	0.005
Sulfonamides	383 (4.2%)	291 (3.7%)	202 (2.9%)	151 (2.1%)	77 (1.6%)	1104 (3.2%)	<.0001 - decrease
Antimyco-bacterials	41 (0.4%)	56 (0.7%)	61 (0.9%)	30 (0.5%)	20 (0.4%)	208 (0.6%)	0.7815

Type of anti-infective drugs used**

Amoxicillin	3529 (38.9%)	2726 (35.1%)	2075 (30.6%)	1679 (29.0%)	1137 (27.5%)	11146 (33.2%)	<.0001 - decrease
Phenoxy-methyl-penicillin	799 (8.8%)	848 (10.9%)	626 (9.2%)	549 (9.4%)	349 (8.4%)	3171 (9.4%)	0.2756
Erythromycin	663 (7.3%)	419 (5.4%)	286 (4.2%)	178 (3.0%)	103 (2.4%)	1649 (4.9%)	<.0001 - decrease
Azithromycin	4 (0.04%)	138 (1.7%)	436 (6.4%)	558 (9.6%)	420 (10.1%)	1556 (4.6%)	<.0001 - increase

Continuation of Table 1

Clarithromycin	418 (4.6%)	330 (4.2%)	308 (4.5%)	267 (4.61%)	177 (4.2 %)	1500 (4.4 %)	0.7643
Ciprofloxacin	288 (3.1%)	272 (3.5%)	260 (3.8%)	249 (4.3%)	229 (5.5%)	1298 (3.8%)	<.0001 - increase
Nitrofurantoin	272 (3.0%)	256 (3.3%)	270 (3.9%)	265 (4.5%)	191 (4.6%)	1254 (3.7%)	<.0001 - increase
Metronidazole	340 (3.7%)	286 (3.6%)	272 (4.0%)	116 (2.0%)	207 (5.0%)	1221 (3.6%)	0.9156
Doxycycline	233 (2.5%)	164 (2.1%)	213 (3.1%)	321 (5.5%)	217 (5.2%)	1148 (3.4%)	<.0001 - decrease
Fluconazole	242 (2.6%)	250 (3.2%)	249 (3.6%)	209 (3.6%)	176 (4.2%)	1126 (3.3%)	<.0001 - increase
Trimethoprime -sufame- toxazole	381 (4.2%)	290 (3.7%)	202 (2.8%)	150 (2.5%)	75 (1.8%)	1098 (3.2%)	<.0001 - decrease
Clindamycine	242 (2.6%)	229 (2.9%)	246 (3.6%)	204 (3.5%)	115 (2.7%)	1036 (3.0%)	0.0444

*Based on the number of pregnant women per year.

** Based on the number of new filled prescriptions.

5.3. EXPOSURE TO ANTI-INFECTIVE DRUGS DURING PREGNANCY AND THE RISK OF PRETERM BIRTH

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5.3.1. ABSTRACT

Objectives: Genitourinary infections during gestation are known risk factors for preterm birth. However, there is still controversy regarding the use of anti-infective drugs for the management of infections related to this condition. The objective of this study was to determine the association between anti-infective exposure during the last two trimesters of pregnancy and the risk of preterm birth.

Methods: We conducted a case-control study within the Quebec Pregnancy Registry. Analyses were done on prospectively collected data on 64618 pregnant women that met eligibility criteria for the study. Use of oral anti-infective drugs during the last two trimesters of pregnancy was the main exposure definition. A case of preterm birth was defined as a delivery occurring before the 37th week of gestation. Controls were defined as deliveries occurring ≥ 37th week. The index date was the date of delivery and the unity of analysis was the pregnant woman. Unconditional logistic regression models were used to generate Odds ratio (OR) along with 95% confidence intervals (95%CI).

Results: The prevalence of preterm birth in the study population was 7.2%. Exposure to all combined anti-infective drugs was associated with a decreased risk of preterm birth (OR=0.78, 95% CI: 0.70-0.88). Use of macrolides was associated with a decreased risk (OR=0.65, 95% CI: 0.50-0.85), whereas the use of metronidazole increased the risk (OR=1.81, 95% CI: 1.30-2.54]). Azithromycin was responsible for a protective effect in women with premature rupture of membranes (OR=0.31, 95% CI: 0.10-0.93).

Conclusion: Physicians must consider therapeutic alternatives to metronidazole in the management of infections that predispose to preterm birth.

5.3.2. INTRODUCTION

Urinary tract infections [7] and bacterial vaginosis (BV) are common during pregnancy, with an incidence of 8% for UTIs and 9% to 20% for BV (1,2). They have been shown to produce both vaginal and systemic immune response and are themselves associated with a high incidence of pelvic inflammatory disease (PID), premature rupture of membranes (PROM), and preterm birth (3). Although the rate of preterm birth has increased in recent years and represents the primary reason for prenatal morbidity and mortality in industrialized countries (4), there is still some controversy regarding the role of anti-infective drugs in the management of infections related to this condition (5). Some studies suggest that a prophylactic anti-infective treatment for inhibiting preterm birth is effective only in women with PROM (6) although there is no consensus as to which would be the best therapeutic choice (7). A Cochrane review concluded that antibiotics routinely administrated during the second or third trimester of pregnancy reduce the risk of preterm birth (8). However, for pregnant women with intact membranes, treatment does not seem to be useful (9). It has also been hypothesised that the type of anti-infective may be important. Commonly recommended bactericidal drugs could cause the release of a microorganism's metabolic products into the genital-urinary internal environment. This effect could trigger the inflammatory pathway leading to preterm birth (10,11). Drugs with a bacteriostatic mechanism of action would have theoretical advantages over bactericidal anti-infective drugs when dealing with infections to avoid preterm birth (12). Several anti-infective classes and administration routes were used in these studies, rendering the application of these findings difficult in the development of specific guidelines. This issue remains controversial (13).

Therefore, the objective of this study was to determine the association between anti-infective exposure during the second and/or third trimester of pregnancy and the risk of preterm birth according to the class and type of anti-infective drug.

5.3.3. METHODS

5.3.3.1. Data Source

We used the Quebec Pregnancy Registry (QPR), built from the linkage of three administrative databases: the *Régie de l'assurance maladie du Québec* (RAMQ), Med-Echo, and the *Institut de la statistique du Québec* (ISQ).

The RAMQ database provides information on medical services dispensed to all residents of Quebec and on prescriptions filled for residents insured by Quebec's Public Prescription Drug Insurance Plan. This database prospectively provides collected data on filled prescriptions, physician-based diagnoses (International Classification of Diseases, ICD-9) (14), therapeutic procedures and the type of institution where the medical procedures were performed, the characteristics of the patient and health care providers, and the costs involved. The RAMQ covers costs for medical services to all Quebec residents and the RAMQ Prescription Drug Plan covers approximately 50% of residents (15), which include persons 65 years and older, welfare recipients and their children, and all workers and their families who do not have access to a private drug insurance program. It is estimated that the medication for 30% of women between 15 and 45 years of age is covered by the RAMQ's drug plan. Access to healthcare services between women covered for their medications by the RAMQ's drug plan and those covered by a private drug plan is similar (16).

The Med-Echo database is a provincial database that records acute care hospitalization data for all Quebec residents, including gestational age. Gestational age is defined from the first day of the last menstrual period to the end of the pregnancy and it is confirmed by ultra-sound around the 18-20th week of gestation.

The ISQ administers the *Fichier des événements démographiques* that provides data on all births and deaths in Quebec. The ISQ database contains demographic information for the mother (date of birth, age, marital status, mother-tongue, place of birth, area of residence, number of live births, number of deliveries), the father (date of birth, age, mother-tongue, place of birth), and the baby (gender, type of delivery, weight, gestational age, order in the family, date of birth).

The linkage between RAMQ and Med-Echo was done using patients' *Numéro d'assurance maladie*, which is a unique identifier for all legal residents in Quebec. The mother-child linkage was possible using the unique identifier that links each baby born to his/her mother in the RAMQ database. The linkage between the RAMQ and ISQ was done using the first name, family name and date of birth of both mother and child.

The Registry contains information on all pregnancies that occurred in Quebec between January 1, 1998 and December 31, 2003. The RAMQ and Med-Echo databases have often been used for epidemiological research leading to articles published in peer-reviewed medical journals (17-19). Data recorded in the RAMQ medication database and in the Med-Echo database have been formally evaluated and found to be comprehensive and valid (20). Medical diagnoses and data recorded in the ISQ databases have also been evaluated and found to be valid and precise (21, 22). The Quebec Pregnancy Registry

has often been used to assess the risks and benefits of drug use during pregnancy (23, 24).

This study was approved by the Sainte-Justine Hospital Ethics Committee, and by the *Commission d'accès à l'information du Québec*, the provincial agency that grants authorization for the use of linked administrative databases (protocol reference #1740).

5.3.3.2. Study Population

Within the Registry, women meeting the following eligibility criteria were included in this study: (1) have between 15 and 45 years of age on the date of entry in the Registry defined as the first day of pregnancy (the first day of last menstrual period); (2) to be continuously insured by the RAMQ drug plan for at least 12 months prior to the first day of gestation and during pregnancy; and (3) gave birth to a live born singleton. The end of the pregnancy was defined as the calendar date of the delivery. If a woman had more than one pregnancy between 1998 and 2003, the first pregnancy meeting eligibility criteria was considered for analysis.

5.3.3.3. Study Design

Within the study population, we conducted a case-control study. Three independent analyses were done: the first assessed the risk of preterm birth for all combined anti-infective drugs; the second assessed the risk for the classes of anti-infective drugs, and the third assessed the risk for individual types of anti-infective drugs.

A case of preterm birth was defined as a delivery occurring before the 37th week of gestation. Controls were defined as deliveries occurring ≥ 37th week.

The index date was the date of delivery and the unity of analysis was the pregnant woman.

5.3.3.4. Assessment of Exposure

In all analyses, exposure to anti-infective drugs was treated dichotomically. We also assessed exposure to at least one anti-infective drug and two or more anti-infectives. Exposure window was the pregnancy's second (>14 to ≤ 26 weeks of gestational age) or third trimester (>26 weeks until delivery). To be considered as exposed in a particular trimester, pregnant women had to have at least one prescription for an anti-infective drug in the corresponding trimester.

For the first analysis, overall exposure to at least one anti-infective drug (all combined) was compared to no exposure. For the second analysis, anti-infective drugs were grouped in the following American Hospital Formulary Service (AHFS) classes: antifongicals (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-infective drugs (AHFS 8:36). The reference category was pregnant women using penicillins (AHFS 8:12:16). For the third analyses, data were collected for the following individual drugs: ampicillin, amoxicillin, azithromycin, ciprofloxacin, clindamycin, doxycycline, erythromycin, fluconazole, metronidazole, nitrofurantoin, and sulfamethoxazole/trimethoprim (SXT).

5.3.3.5. Covariates

The following variables were considered as potential confounders of the association between exposure and the risk of preterm birth, and were measured in the year before and during pregnancy: number of different types of medications used other than anti-infective, number of different prescribers for all medications, number of visits to the physician, visits to the emergency department and/or hospitalizations, diabetes (ICD-9 codes 250-259, 271.4, 790.2 and the filling of prescriptions for medications for diabetes), asthma (ICD-9 codes 493.0, 493.1, 493.9 and the filling of prescriptions for any anti-asthmatic drugs), hypertension (ICD-9 codes 640-642 and the filling of prescriptions for any antihypertensive drugs), infections (ICD-9 codes 001-136), respiratory tract infections (ICD-9 codes 460-466, 472-487), urinary tract and sexually transmitted infections ((UT and STI) ICD-9 codes 590, 599-599.6), PID (ICD-9 codes 614-616), diseases of the female genital tract (ICD-9 codes 617-619). We also determined the following socio-economic variables on index date: maternal age, maternal place of residence (urban versus rural), maternal RAMQ drug plan status (adherent versus welfare recipient), and calendar year of the pregnancy.

5.3.3.6. Statistical and Sensitivity Analysis

Descriptive statistics were used to compare cases and controls. Student t-tests and Chi-square tests were used to examine the differences between the two groups for continuous and categorical data, respectively. Some women may have been diagnosed with an infection after recognition of a pregnancy complication such as PROM and treated in the hospital just prior to giving birth. Since we relied on outpatient pharmacy records to ascertain exposure, such a group of women would have erroneously been considered as non-exposed. To counter this potential bias, we repeated the three analyses for

the group of women with a diagnosis of UT/STI and PROM. Univariate and multivariable unconditional logistic regression models were built, adjusting for important confounders and proxy variables for socioeconomic, health services utilization and co-morbidities. Consistency of the model was evaluated by Hosmer-Lemeshow goodness of fit test. Results were expressed in adjusted odds ratios (OR) along with 95% confidence intervals (95% CI). SAS version 9.1 (SAS Institute, Cary, NC) was used to conduct all analyses.

5.3.4. RESULTS

5.3.4.1. Characteristics of the Study Population

64618 pregnant women within the Quebec Pregnancy Registry met the eligibility criteria. The mean age of the study population was 27.4 (standard deviation 5.9 years), 35% of women were welfare recipients and 80% lived in an urban area on the index date. The prevalence of preterm birth was 7.2%. Cases were 28% more likely to be welfare recipients at the index date when compared to controls (Table 1).

5.3.4.2. Exposure to an Anti-infective Drug and the Risk for Preterm birth

The use of anti-infective drugs during the second or third trimesters of pregnancy was slightly higher among controls (18.7%) than among cases (17.8%). Exposure to all combined anti-infective drugs during these periods was a protective factor for preterm birth (adjusted OR=0.78 [95%CI: 0.70, 0.88]) (Table 2).

5.3.4.3. Classes and Types of Anti-infective Drugs and the Risk of Preterm birth

Penicillins and macrolides were significantly associated with a decreased risk of preterm birth (adjusted OR=0.65 [95%CI: 0.53, 0.82] and adjusted OR=0.65 [95%CI: 0.50, 0.85], respectively, Table 3 and 4). Amoxicillin (adjusted OR=0.78 [95%CI: 0.70, 0.87]) and erythromycin (adjusted OR=0.76 [95%CI: 0.61, 0.95]) both reduced the risk of preterm birth when the reference group had no exposure to such drugs, while metronidazole was associated with an 81% increase in the risk (adjusted OR=1.81 [95%CI: 1.30, 2.54], Table 5).

5.3.4.5. Analysis in the Subgroup of Women with a Diagnosis for UT/STI and PROM

We identified 17052 women with a diagnosis of UT/STI (prevalence of preterm birth: 9.75%) and 9325 women with a diagnosis of PROM (prevalence of preterm birth: 18.25%, Table 6). In the UT/STI subgroup, exposure to penicillins was protective for preterm birth (adjusted OR=0.84 [95%CI: 0.72, 0.99]), whereas metronidazole was associated with an almost three-fold increase in the risk (adjusted OR=2.80 [95%CI: 1.65, 4.71]). Women with a diagnosis of PROM and who were exposed to macrolides were more protected against preterm birth (adjusted OR=0.61 [95%CI: 0.41, 0.90]). Azithromycin was responsible for this protective effect (adjusted OR=0.31 [95%CI: 0.10, 0.93], Table 6).

5.3.5. DISCUSSION

The prevalence of preterm birth in our study population is lower than the proportion in the Canadian population (8.2%) (25), and in the USA (12.8%) (26), and is similar to the proportion reported in Europe (5-9%) (27). In spite of medical advances in the area of prenatal care, the annual rate of preterm birth is increasing (28). Some explanations for this trend include the use of obstetric interventions, increasing rates of multiplicity (29), and older maternal age. Our data suggest that factors related to a lower socio-economic and health status in the year before and during pregnancy, may be targets for preventive interventions in the course of pregnancy. Our findings are corroborated by other studies (4,26,30,31).

Maternal infections are related to 40% of the cases of preterm birth (32). However, there is some controversy when considering anti-infective drugs to reduce the risk of preterm birth with respect to the best therapeutic choice (5). Our data suggest that women treated with anti-infective drugs during the second or third trimester of pregnancy have a 22% decrease in the risk of having a preterm delivery. The decrease in the risk was more evident for women taking at least two anti-infectives. Two meta-analyses of randomized clinical trials (RCTs) that compared all combined antibiotics with placebo or no treatment, failed to demonstrate a significant reduction in the risk of preterm birth (8;33). In spite of the overall quality of RCTs included in these studies, these meta-analyses could have lacked power to assess a random protective effect of several classes of anti-infective drugs combined together. As different anti-infective drugs act trough different action mechanisms, this could have influenced these results.

In our study, macrolides and penicillins were significantly associated with a 35% reduction in the risk of preterm birth. Results from others studies

corroborate our findings of a beneficial effect of treatment with amoxicillin or erythromycin in the management of infections that predispose to preterm birth. However, the results of a recent RCT (34) provide evidence against antibiotic treatment of asymptomatic women: there was an increase in the risk of cerebral palsy in children of women with intact membranes who received amoxicillin or erythromycin to avoid preterm birth. Others studies have showed the benefits of erythromycin in reducing the risk of preterm birth compared to placebo (6,13) and the combination of this drug with clindamycin has already been proposed (13,35,36), although the literature concerning this regimen is conflicting (33).

Macrolides appears to be more protective in reducing preterm birth, compared to penicillins. We believe that the principal reason for this difference is the mechanism of action. Macrolides are bacteriostatic, whereas penicillins are bactericidals. Treatment of infections with bactericidal drugs is associated with the release of endotoxins from bacteriolysis, causing a local vaginal inflammatory response and possibly, resulting in preterm birth (13). Our analysis shows bacteriostatic drugs to be protective for preterm birth, after adjustment for others variables. However, the 95% confidence intervals of the point estimate for each class tend to overlap. Further research is required to address this question.

Another finding in favor to the bacteriostatic hypothesis is that our results showed an increased risk of preterm birth after use of metronidazole. Several studies are in agreement with this result (13, 37-39). Furthermore, others studies were unable to demonstrate a clear benefit of metronidazole in preventing preterm birth (33,40). Despite the evidence against the use of metronidazole to treat women at risk for preterm birth, this drug is currently indicated for the treatment of bacterial vaginosis (41). Metronidazole is able to promote artificial selection of lactobacilli in the vaginal environment, allowing

a non-competitive growth of harmful microorganisms, ascending infection, stimulation of a local inflammatory process, and early delivery (42).

Finally, a noteworthy finding was the effect of azithromycin in women with a diagnosis of UT/STI and PROM. This drug was associated with a reduction of 70% in the risk of preterm birth in the PROM subgroup. This result indicates that azithromycin can be an effective alternative candidate to erythromycin in women with PROM. Erythromycin became the preferred choice for women with PROM, after the evidence linking amoxicillin/clavulanate (formerly the first choice for this condition) with neonatal necrotising enterocolitis (43). Since then, the widespread use of erythromycin has been responsible for an increase in bacterial resistance and resulting reduction in its efficacy (44). Both drugs have a similar mechanism of action, thought azithromycin has some advantages over erythromycin: better efficacy, broader spectra, and better tolerability (45). However, to date, there are no sound studies that have evaluated the risk of azithromycin on adverse pregnancy outcomes. To our knowledge, this is the first study that relates azithromycin to a significant decrease in the risk of preterm birth. Our results may encourage physicians to consider the use of this drug as an alternative in the management of infections that predispose to preterm birth.

This study was conducted on a large sample of pregnant women obtained from administrative databases and thus, we were able to adjust for several variables related to anti-infective drug use and the risk of preterm birth. The assessment of exposure in studies using administrative databases offers the advantage of avoiding recall bias, a major source of potential bias in observational research. We were able to obtain information on classes and types of anti-infective drugs according to prescriptions.

Dispensing of a prescription does not mean that a patient actually took the medication or was completely compliant with treatment. However, the provincial drug plan requires that the beneficiary pay a portion of the costs for medications. This increases the likelihood that prescriptions that are filled are in fact consumed. Data were not available for pregnant women who did not use the public healthcare system. However, given the free universal system in Québec, we do not believe that this would confound our results, but this could affect the generalizability of some findings that may be more strongly associated with socio-demographic factors that could act as an effect modifier (16). Similarly, data are not available for anti-infective exposure for more severe infections in hospital setting. Furthermore, multiple testing could partially explain some of our findings.

5.3.6. CONCLUSION

In conclusion, our study showed that the use of anti-infective drugs during the second or third trimester of pregnancy was significantly associated with a reduced risk of preterm birth. Drugs with a bacteriostatic mechanism of action seem to be more effective in avoiding preterm birth, although more data are required to clarify this issue. Treatment with metronidazole should be revised in women with a higher risk of preterm birth. Azithromycin may be an efficient choice in the management of infections that predispose to preterm birth.

5.3.7. REFERENCES

1. Macejko AM, Schaeffer AJ. Asymptomatic bacteriuria and symptomatic urinary tract infections during pregnancy. Urologic Clinics of North America 2007;34:35-42.

2. Guise JM, Mahon SM, Aickin M, Helfand M, Peipert JF, Westhoff C. Screening for bacterial vaginosis in pregnancy. American Journal of Preventive Medicine 2001;20:62-72.

3. Czeizel AE, Rockenbauer M, Olsen J. Use of antibiotics during pregnancy. European Journal of Obstetrics & Gynecology and Reproductive Biology 1998;81:1-8.

4. Steer P. The epidemiology of preterm labour. British Journal of Obstetritics and Gynaecology 2005;112 Suppl 1:1-3.

5. Lamont RF. Can antibiotics prevent preterm birth--the pro and con debate. British Journal of Obstetritics and Gynaecology 2005;112 Suppl 1:67-73.

6. Kenyon S, Boulvain M, Neilson J. Antibiotics for preterm rupture of the membranes: a systematic review. Obstetritics and Gynaecology 2004;104:1051-1057.

7. Waters TP, Mercer BM. The management of preterm premature rupture of the membranes near the limit of fetal viability. American Journal of Obstetritics and Gynecology 2009;201:230-240.

8. Thinkhamrop J, Hofmeyr GJ, Adetoro O, Lumbiganon P. Prophylactic antibiotic administration in pregnancy to prevent infectious morbidity and mortality. Cochrane Database Systematic Reviews 2002;CD002250.

9. King J, Flenady V. Prophylactic antibiotics for inhibiting preterm labour with intact membranes. Cochrane Database Systematic Reviews 2002;CD000246.

10. Locksmith G, Duff P. Infection, antibiotics, and preterm delivery. Seminars in Perinatology 2001;25:295-309.

11. McGregor JA, French JI. Preterm Birth: The Role of Infection and Inflammation. Medscape Womens Health 1997;2:1.

12. Goodwin J, Rieder S, Rieder MJ, Matsui D. Counseling regarding pregnancy--related drug exposures by family physicians in Ontario. Canadian Journal of Clinical Pharmacology 2007;14:e58-e69.

13. Morency AM, Bujold E. The effect of second-trimester antibiotic therapy on the rate of preterm birth. Journal of obstetrics and gynaecology Canada 2007;29:35-44.

14. World Health Organization. International Classification of Diseases. 1997.

15. Régie de l'assurance maladie du Québec: Statistiques annuelles. 1997.

16. Berard A, Lacasse A. Validity of perinatal pharmacoepidemiologic studies using data from the RAMQ administrative database. Canadian Journal of Clinical Pharmacology 2009;16(2):e360-369.

17. Blais L, Desgagne A, LeLorier J. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and the risk of cancer: a nested case-control study. Archives of Internal Medicine 2000;160:2363-2368.

18. Garbe E, LeLorier J, Boivin JF, Suissa S. Risk of ocular hypertension or open-angle glaucoma in elderly patients on oral glucocorticoids. Lancet 1997;350:979-982.

19. Avorn J, Monette J, Lacour A, Bohn RL, Monane M, Mogun H et al. Persistence of use of lipid-lowering medications: a cross-national study. The Journal of the American Medical Association 1998;279:1458-1462.

20. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. Journal of Clinical Epidemiology 1995;48:999-1009.

21. Vilain A, Otis S, Forget A, Blais L. Agreement between administrative databases and medical charts for pregnancy-related variables among asthmatic women. Pharmacoepidemiology and Drug Safety 2008;17:345-353.

22. Levy AR, Mayo NE, Grimard G. Rates of transcervical and pertrochanteric hip fractures in the province of Quebec, Canada, 1981-1992. American Journal of Epidemiology 1995;142:428-436.

23. Ramos E, Oraichi D, Rey E, Blais L, Berard A. Prevalence and predictors of antidepressant use in a cohort of pregnant women. British Journal of Obstetritics and Gynaecology 2007;114:1055-1064.

24. Berard A, Azoulay L, Koren G, Blais L, Perreault S, Oraichi D. Isotretinoin, pregnancies, abortions and birth defects: a population-based perspective. British Journal of Clinical Pharmacology 2007;63:196-205.

25. Public Health Agency of Canada. Canadian Perinatal Health Report 2008. Ottawa: Ministry of Health; 2008.

26. Reedy NJ. Born too soon: the continuing challenge of preterm labor and birth in the United States. Journal of Midwifery and Womens Health 2007;52:281-290.

27. Slattery MM, Morrison JJ. Preterm delivery. Lancet 2002;360:1489-1497.

28. Alexander GR, Slay M. Prematurity at birth: trends, racial disparities, and epidemiology. Mental retardation and developmental disabilities research reviews 2002;8:215-220.

29. Perri T, Chen R, Yoeli R, Merlob P, Orvieto R, Shalev Y et al. Are singleton assisted reproductive technology pregnancies at risk of prematurity? Journal of Assisted Reproduction and Genetics 2001;18:245-249.

30. Damus K. Prevention of preterm birth: a renewed national priority. Current Opinion in Obstetrics & Gynecology 2008;20:590-596.

31. Field T, Diego M, Hernandez-Reif M. Prematurity and potential predictors. The International journal of neuroscience 2008;118:277-289.

32. Lettieri L, Vintzileos AM, Rodis JF, Albini SM, Salafia CM. Does "idiopathic" preterm labor resulting in preterm birth exist? American Journal of Obstetrics and Gynecology 1993;168:1480-1485.

33. Simcox R, Sin WT, Seed PT, Briley A, Shennan AH. Prophylactic antibiotics for the prevention of preterm birth in women at risk: a meta-analysis. Australian and New Zealand Journal of Obstetrics and Gynaecology 2007;47:368-377.

34. Kenyon S, Pike K, Jones DR, Brocklehurst P, Marlow N, Salt A et al. Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial. Lancet 2008;372:1319-1327.

35. Lamont RF. Antibiotics used in women at risk of preterm birth. American Journal of Obstetrics and Gynecology 2008;199:583-584.

36. Lamont RF, Duncan SL, Mandal D, Bassett P. Intravaginal clindamycin to reduce preterm birth in women with abnormal genital tract flora. Obstetrics & Gynecology 2003;101:516-522.

37. Shennan A, Crawshaw S, Briley A, Hawken J, Seed P, Jones G et al. A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervicovaginal fetal fibronectin: the PREMET Study. The British Journal of Obstetrics & Gynaecology 2006;113:65-74.

38. Odendaal HJ, Popov I, Schoeman J, Smith M, Grove D. Preterm labour-is bacterial vaginosis involved? South African medical journal 2002;92:231-234.

39. Klebanoff MA, Carey JC, Hauth JC, Hillier SL, Nugent RP, Thom EA et al. Failure of metronidazole to prevent preterm delivery among pregnant women with asymptomatic Trichomonas vaginalis infection. The New England Journal of Medicine 2001;345:487-493.

40. Mann JR, McDermott S, Zhou L, Barnes TL, Hardin J. Treatment of trichomoniasis in pregnancy and preterm birth: an observational study. Journal of Womens Health 2009;18:493-497.

41. Guidelines. Antimicrobial Therapy - A Concise Canadian Guide 2007. Montreal: Prism, 2007.

42. Wilks M, Wiggins R, Whiley A, Hennessy E, Warwick S, Porter H et al. Identification and H(2)O(2) production of vaginal lactobacilli from pregnant women at high risk of preterm birth and relation with outcome. Journal of Clinical Microbiology 2004;42:713-717.

43. Kenyon, S. L. Taylor D. J. Tarnow-Mordi W. Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomized trial. The Lancet 2001 357(9261), 979-988.

44. Shennan AH, Chandiramani M. Antibiotics for spontaneous preterm birth. British Medical Journal 2008;337:a3015.

45. Piscitelli SC, Danziger LH, Rodvold KA. Clarithromycin and azithromycin: new macrolide antibiotics. Clinical Pharmacology 1992;11:137-152.

Table 1. Characteristics and health status of the study population.

Variables	Cases* *(n=4650) (7.2%)*	Controls** *(n=59968) (92.8%)*	Crude OR [*95% CI*]	Adjusted OR[b] [*95% CI*]
Maternal characteristics at the index date				
Maternal age	27.4 (5.9)	27.3 (5.5)	1.00 [0.99, 1.00]	1.01 [0.99, 1.02]
Place of birth				
Rural	1053 (22.6)	14050 (23.4)	1.00 (reference)	1.00 (reference)
Urban	3597 (77.3)	45918 (76.5)	1.04 [0.97, 1.12]	0.99 [0.91, 1.06]
RAMQ Insurance Status				
Adherents	2803 (62.2)	39842 (69.0)	1.00 (reference)	1.00 (reference)
Welfare recipients	1704 (37.8)	17831 (30.9)	1.36 [1.27, 1.44]	1.28 [1.19, 1.36]
Health Status and medication use before pregnancy				
Number of different medications used				
0-2	3162 (68.0)	44028 (73.4)	1.00 (reference)	1.00 (reference)
3-5	1072 (23.0)	12170 (20.3)	1.23 [1.14, 1.31]	1.21 [1.10, 1.33]
≥ 6	416 (8.9)	3770 (6.2)	1.53 [1.38, 1.71]	1.31 [1.12, 1.52]

Number of different prescribers before pregnancy				
0-2	3239 (69.6)	43595 (72.7)	1.00 (reference)	1.00 (reference)
≥ 3	1411 (30.3)	16373 (27.3)	1.16 [1.08, 1.23]	0.94 [0.85, 1.04]
Emergency department visit/hospitalization				
No	3888 (83.6)	51365 (85.6)	1.00 (reference)	1.00 (reference)
Yes	762 (16.4)	8603 (14.3)	1.16 [1.10, 1.22]	1.02 [0.93, 1.12]
Physician visits before pregnancy				
0-2	125 (2.7)	997 (1.6)	1.00 (reference)	1.00 (reference)
3-5	258 (5.5)	2044 (3.4)	1.00 [0.80, 1.26]	0.92 [0.72, 1.17]
≥6	4267 (91.7)	56927 (94.9)	0.60 [0.49, 0.72]	0.41 [0.33, 0.50]
Comorbidities				
Infections	566 (12.1)	6556 (10.9)	1.13 [1.03, 1.23]	1.08 [0.97, 1.19]
Respiratory tract infections	1053 (22.5)	14236 (23.7)	0.94 [0.87, 1.01]	0.92 [0.85, 1.00]
Urinary tract and sexually transmitted infections	344 (7.4)	3572 (5.9)	1.26 [1.12, 1.41]	1.12 [0.99, 1.27]
Pelvic inflammatory disease	519 (11.6)	6090 (10.1)	1.11 [1.01, 1.22]	1.07 [0.97, 1.18]
Diseases of the female genital tract	1011 (21.7)	11583 (19.3)	1.16 [1.08, 1.25]	1.07 [0.99, 1.16]

Asthma	673 (14.4)	7510 (12.5)	1.18 [1.08, 1.30]	0.99 [0.90, 1.09]
Diabetes	85 (1.8)	551 (0.9)	2.00 [1.60, 2.52]	1.40 [1.08, 1.81]
Hypertension	97 (2)	695 (1.1)	1.82 [1.46, 2.25]	1.02 [0.80, 1.30]
Health Status and medication use during pregnancy				
Number of different medications used				
0-2	3720 (80.0)	50302 (83.8)	1.00 (reference)	1.00 (reference)
3-5	682 (14.6)	7804 (13.0)	1.18 [1.08, 1.30]	1.00 [0.90, 1.12]
≥ 6	248 (5.3)	1862 (3.1)	1.80 [1.57, 2.06]	1.14 [0.94, 1.37]
Number of different prescribers				
0-2	3826 (82.3)	51110 (85.2)	1.00 (reference)	1.00 (reference)
≥ 3	824 (17.7)	8858 (14.7)	1.24 [1.15, 1.34]	0.98 [0.87, 1.09]
Emergency department visit/hospitalisation				
No	152 (3.2)	7588 (12.6)	1.00 (reference)	1.00 (reference)
Yes	4498 (96.7)	52380 (87.3)	1.90 [1.81, 1.98]	4.58 [3.86, 5.43]

Comorbidities				
Infections	539 (11.6)	6458 (10.7)	1.08 [0.98, 1.19]	0.95 [0.85, 1.05]
Respiratory tract infections	647 (13.9)	9036 (15.0)	0.91 [0.83, 0.99]	0.92 [0.85, 1.02]
Urinary tract and sexually transmitted infections	1665 (35.8)	15387 (25.6)	1.61 [1.52, 1.72]	1.50 [1.40, 1.60]
Pelvic inflammatory disease	299 (6.4)	4514 (7.5)	0.84 [0.75, 0.95]	1.12 [0.58, 2.18]
Diseases of the female genital tract	996 (21.4)	11518 (19.2)	1.15 [1.06, 1.23]	1.08 [1.00, 1.17]
Asthma	825 (17.4)	7101 (11.8)	1.60 [1.48, 1.73]	1.24 [1.13, 1.36]
Diabetes	320 (6.8)	3099 (5.1)	1.35 [1.20, 1.53]	1.02 [0.89, 1.17]
Hypertension	617 (13.2)	3119 (5.2)	2.80 [2.54, 3.05]	2.37 [2.14, 2.62]
Visit to an Obstetrician or Gynecologist, n (%)				
No	518 (11.2)	13569 (22.6)	1.00 (reference)	1.00 (reference)
Yes	4132 (88.8)	46399 (77.3)	2.33 [2.12, 2.56]	2.03 [1.85, 2.25]

Number of prenatal visits, n (%)				
0-5	1522 (32.7)	11273 (18.8)	1.00 (reference)	1.00 (reference)
6-11	2652 (57)	33045 (55.1)	0.60 [0.55, 0.63]	0.50 [0.45, 0.53]
≥12	476 (10.2)	15650 (26.1)	0.22 [0.20, 0.25]	0.16 [0.15, 0.18]

*Percentages may not add up to 100% due to rounding.

**Adjusted for calendar year of pregnancy

Table 2. Exposure to anti-infective drugs and the risk of preterm birth

Variables	**Cases*** *(n=4650)* *(7.2%)*	**Controls*** *(n=59 968)* *(92.8%)*	**Crude OR** [*95% CI*]	**Adjusted OR**** [*95% CI*]
Anti-infective Drug use				
Anti-infective use during the second and/or the third trimesters of pregnancy				
No	3823 (82.2)	48759 (81.3)	1.00 (reference)	1.00 (reference)
Yes	827 (17.8)	11209 (18.7)	0.94 [0.87, 1.01]	0.78 [0.70, 0.88]
At least 1 anti-infective drug	666 (14.3)	9043 (15)	0.93 [0.86, 1.02]	0.86 [0.79, 0.95]
2 or more anti-infective drugs	161 (3.3)	2166 (3.6)	0.90 [0.76, 1.07]	0.79 [0.66, 0.95]
Anti-infective use before pregnancy				
No	2788 (60.0)	36487 (60.8)	1.00 (reference)	1.00 (reference)
Yes	1862 (40.0)	23481 (39.1)	1.03 [0.97, 1.10]	0.95 [0.88, 1.03]

Anti-infective use any point during pregnancy				
No	3366 (72.4)	43753 (72.9)	1.00 (reference)	1.00 (reference)
Yes	1284 (27.6)	16215 (27.0)	1.02 [0.96, 1.10]	1.08 [0.97, 1.20]
Anti-infective use during the first trimester of pregnancy				
No	3935 (84.6)	52130 (86.9)	1.00 (reference)	1.00 (reference)
Yes	715 (15.3)	7838 (13)	1.20 [1.11, 1.31]	1.13 [1.03, 1.24]

*Percentages may not add up to 100% due to rounding.

**Analysis adjusted for all the variables present in Table 1, and calendar date.

Table 3. Exposure to anti-infective drugs and the risk of preterm birth – analysis by class.

Variables	Cases* *(n=4650) (7.2%)*	Controls* *(n=59968) (92.8%)*	Crude OR [*95% CI*]	Adjusted OR** [*95% CI*]
Anti-infective Drugs use by Pharmacological Class – 2nd or 3rd trimester				
Antimycobacterials				
No	4645 (99.8)	59963 (99.9)	1.00 (reference)	1.00 (reference)
Yes	5 (0.11)	32 (0.1)	2.01 [0.78, 5.17]	1.64 [0.62, 4.32]
Antimycotics				
No	4630 (99.5)	59786 (99.7)	1.00 (reference)	1.00 (reference)
Yes	20 (0.5)	182 (0.3)	1.42 [0.90, 2.25]	1.33 [0.82, 2.15]
Cephalosporins				
No	4560 (98.1)	58894 (99.2)	1.00 (reference)	1.00 (reference)
Yes	90 (1.9)	1074 (1.8)	1.08 [0.87, 1.34]	0.93 [0.74, 1.17]
Macrolides				
No	4538 (97.6)	58241 (99.8)	1.00 (reference)	1.00 (reference)
Yes	112 (2.4)	1727 (2.8)	0.83 [0.68, 1.01]	0.65 [0.50, 0.85]
Penicillins				
No	4119 (88.5)	52161 (87.0)	1.00 (reference)	1.00 (reference)
Yes	531 (11.4)	7807 (13.0)	0.86 [0.78, 0.94]	0.65 [0.53, 0.82]

Quinolones				
No	4631 (99.5)	59650 (99.5)	1.00 (reference)	1.00 (reference)
Yes	19 (0.5)	318 (0.5)	0.77 [0.5, 1.22]	0.97 [0.46, 2.05]
Sulfonamides				
No	4639 (99.8)	59750 (99.6)	1.00 (reference)	1.00 (reference)
Yes	11 (0.2)	218 (0.4)	0.65 [0.35, 1.19]	0.60 [0.22, 1.55]
Tetracyclines				
No	4649 (99.9)	59920 (99.9)	1.00 (reference)	1.00 (reference)
Yes	1 (0.1)	48 (0.1)	0.27 [0.04, 1.95]	0.36 [0.05, 2.64]
Urinary anti-infectives				
No	4563 (98.1)	59068 (98.5)	1.00 (reference)	1.00 (reference)
Yes	87 (1.9)	900 (1.5)	1.25 [1.00, 1.56]	0.95 [0.73, 1.25]
Others				
No	4610 (99.1)	59552 (99.3)	1.00 (reference)	1.00 (reference)
Yes	40 (0.8)	416 (0.7)	1.24 [0.90, 1.72]	1.17 [0.84, 1.63]

*Percentages may not add up to 100% due to rounding.

**Analysis adjusted for all the variables present in Table 1, and calendar date.

Table 4. Exposure to anti-infective drugs and the risk of preterm birth – class analysis, reference: penicillin

Variables	Cases* *(n=4650) (7.2%)*	Controls* *(n=59968) (92.8%)*	Crude OR [*95% CI*]	Adjusted OR** [*95% CI*]
Classes				
Antimycobacterials	5 (0.11)	20 (0.03)	3.73 [1.40, 9.98]	2.63 [0.94, 7.40]
Antimycotics	8 (0.17)	94 (0.16)	1.27 [0.61, 2.62]	1.25 [0.58, 2.66]
Cephalosporins	49 (1.05)	573 (0.96)	1.27 [0.93, 1.73]	1.22 [0.88, 1.67]
Macrolides	80 (1.72)	1204 (2.01)	0.99 [0.77, 1.26]	0.92 [0.72, 1.19]
Penicillins	455 (9.7)	6777 (11.3)	1.00 (reference)	1.00 (reference)
Quinolones	4 (0.09)	40 (0.07)	1.50 [0.53, 4.20]	1.61 [0.55, 4.71]
Tetracyclines	1 (0.02)	31 (0.05)	0.48 [0.06, 3.52]	0.50 [0.06, 3.70]
Urinary anti-infectives	52 (1.12)	551 (0.92)	1.40 [1.04, 1.90]	1.30 [0.95, 1.77]
Others	27 (0.60)	267 (0.40)	1.50 [1.00, 2.26]	1.41 [0.92, 2.15]

*Percentages may not add up to 100% due to rounding.

**Analysis adjusted for all the variables present in Table 1, and calendar date.

Table 5. Exposure to anti-infective drugs and the risk of preterm birth – individual drugs analysis.

Effect of individual drugs	**Cases*** *(n=4650) (7.2%)*	**Controls*** *(n=59968) (92.8%)*	**Crude OR** [*95% CI*]	**Adjusted OR**** [*95% CI*]
Ampicillin	11 (0.24)	113 (0.2)	1.25 [0.67, 2.33]	1.17 [0.62, 2.19]
Amoxicillin	435 (9.35)	6391 (10.6)	0.86 [0.78, 0.95]	0.78 [0.70, 0.87]
Azithromycin	26 (0.56)	392 (0.65)	0.85 [0.57, 1.27]	0.79 [0.52, 1.18]
Ciprofloxacin	8 (0.17)	84 (0.14)	1.23 [0.56, 2.54]	1.15 [0.54, 2.44]
Clindamicin	35 (0.75)	328 (0.5)	1.38 [0.97, 1.95]	1.27 [0.90, 1.82]
Doxyciclin	1 (0.02)	21 (0.04)	0.61 [0.08, 4.56]	0.80 [0.10, 6.40]
Erythromycin	90 (1.95)	1374 (2.3)	0.84 [0.68, 1.04]	0.76 [0.61, 0.95]
Fluconazole	13 (0.28)	109 (0.2)	1.55 [0.87, 2.74]	1.40 [0.76, 2.52]
Metronidazole	41 (0.88)	287 (0.5)	1.85 [1.33, 2.57]	1.81 [1.30, 2.54]
Nitrofurantoin	87 (1.9)	900 (1.5)	1.25 [1.00, 1.56]	1.06 [0.84, 1.33]
Trimethoprim/ Sulfamethoxazole	11 (0.24)	213 (0.36)	0.66 [0.36, 1.22]	0.60 [0.32, 1.10]

*Percentages may not add up to 100% due to rounding. **Analysis adjusted for all the variables present in Table 1, and calendar date.

Table 6. Exposure to anti-infective drugs and the risk of preterm birth - UTI and PROM subgroup analysis.

Variables	UTI/STI (n=17 052, cases=9.75%)*		PROM (n=9 325, cases=18.25%)*	
	Crude OR [*95% CI*]	Adjusted OR** [*95% CI*]	Crude OR [*95% CI*]	Adjusted OR** [*95% CI*]
Anti-infective Drugs use by Pharmacological Class – 2nd or 3rd trimester (reference: no exposure to the respective class)				
Anti-infective use during the second and/or the third trimesters of pregnancy	0.96 [0.85, 1.10]	1.10 [0.85, 1.43]	0.98 [0.86, 1.13]	0.90 [0.76, 1.05]
Anti-mycobacterials	1.23 [0.28, 5.40]	1.47 [0.32, 6.73]	2.25 [0.20, 24.7]	2.35 [0.19, 28.3]
Antimycotics	1.52 [0.82, 2.81]	1.57 [0.81, 3.06]	1.80 [0.80, 4.08]	1.65 [0.66, 4.08]
Cephalosporins	1.19 [0.90, 1.60]	1.14 [0.83, 1.55]	1.07 [0.71, 1.61]	1.04 [0.67, 1.62]
Macrolides	0.90 [0.67, 1.20]	0.84 [0.62, 1.15]	0.70 [0.48, 1.02]	0.61 [0.41, 0.90]
Penicillins	0.84 [0.73, 0.98]	0.84 [0.72, 0.99]	0.98 [0.83, 1.16]	0.91 [0.76, 1.10]
Quinolones	0.70 [0.35, 1.27]	0.93 [0.35, 2.50]	0.62 [0.24, 1.58]	1.20 [0.32, 4.56]
Sulfonamides	0.48 [0.19, 1.19]	0.42 [0.11, 1.63]	0.35 [0.08, 1.50]	0.25 [0.03, 1.80]
Tetracyclines	0.77 [0.10, 6.0]	0.84 [0.09, 7.88]	2.25 [0.20, 24.7]	1.35 [0.10, 17.6]
Urinary anti-infectives	1.12 [0.85, 1.50]	1.23 [0.91, 1.66]	1.05 [0.69, 1.60]	0.99 [0.63, 1.55]
Others	0.85 [0.50, 1.51]	0.73 [0.40, 1.32]	1.18 [0.65, 2.13]	1.07 [0.58, 2.00]

Anti-infective Drugs use by Pharmacological Class – 2nd or 3rd trimester (reference: exposure to penicillins)				
Anti-mycobacterials	1.80 [0.21, 15.0]	1.80 [0.16, 19.8]	4.61 [0.28, 74.1]	3.75 [0.22, 64.2]
Antimycotics	1.85 [0.76, 4.45]	1.84 [0.72, 4.66]	0.77 [0.17, 3.46]	1.26 [0.26, 6.10]
Cephalosporins	1.65 [1.10, 2.49]	1.40 [0.90, 2.16]	1.12 [0.63, 1.98]	1.10 [0.60, 2.01]
Macrolides	2.15 [0.47, 9.9]	2.14 [0.44, 10.4]	0.50 [0.29, 0.85]	0.46 [0.26, 0.81]
Penicillins	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quinolones	0.83 [0.10, 6.37]	0.67 [0.08, 5.42]	1.15 [0.12, 10.4]	1.39 [0.14, 13.7]
Sulfonamides*	1.25 [0.87, 1.80]	1.14 [0.78, 1.67]	***	***
Tetracyclines	1.54 [0.18, 12.6]	2.13 [0.23, 19.4]	2.30 [0.20, 25.5]	1.47 [0.11, 19.7]
Urinary anti-infectives	1.24 [0.82, 1.86]	1.24 [0.80, 1.90]	0.85 [0.48, 1.52]	0.80 [0.44, 1.47]
Others	1.02 [0.49, 2.15]	0.88 [0.40, 1.91]	1.21 [0.60, 2.48]	1.30 [0.62, 2.76]
Anti-infective Drugs use by Individual drug – 2nd or 3rd trimester				
Amoxicillin	0.88 [0.76, 1.03]	0.90 [0.75, 1.06]	0.95 [0.80, 1.14]	0.87 [0.70, 1.08]
Ampicillin	0.72 [0.26, 2.00]	1.03 [0.35, 2.97]	1.72 [0.61, 4.84]	2.97 [0.93, 9.48]
Azithromycin	0.95 [0.55, 1.65]	0.88 [0.50, 1.60]	0.71 [0.35, 1.45]	0.31 [0.10, 0.93]
Ciprofloxacin	1.12 [0.44, 2.85]	1.00 [0.36, 2.77]	1.50 [0.40, 5.51]	1.40 [0.13, 14.7]
Clindamycin	0.94 [0.50, 1.75]	0.77 [0.40, 1.48]	1.11 [0.57, 2.17]	1.19 [0.55, 2.58]
Doxyciclin*	1.54 [0.18, 12.8]	1.12[0.09, 13.9]	***	***
Erythromycin	0.92 [0.66, 1.27]	0.88 [0.62, 1.25]	0.67 [0.44, 1.03]	0.61 [0.36, 1.04]
Fluconazole*	1.70 [0.83, 3.47]	1.64 [0.75, 3.56]	***	***
Metronidazole	2.7 [1.67, 4.35]	2.80 [1.65, 4.71]	2.45 [1.37, 4.36]	1.87 [0.97, 3.62]

Nitrofurantoin	1.12 [0.85, 1.50]	1.21 [0.90, 1.64]	1.05 [0.69, 1.60]	0.73 [0.42, 1.29]
Trimethoprim-sulfamethoxazole	0.50 [0.20, 1.23]	0.42 [0.16, 1.09]	0.37 [0.08, 1.57]	0.52 [0.11, 2.36]

*Percentages may not add up to 100% due to rounding.

**Analysis adjusted for all the variables present in Table 1, and calendar date.

***No data available for the PROM subgroup.

5.4. EXPOSURE TO ANTI-INFECTIVE DRUGS AND THE RISK OF SMALL-FOR-GESTATIONAL-AGE NEWBORNS: A CASE-CONTROL STUDY

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5.4.1. ABSTRACT

Objective: To determine the association between anti-infective exposure during the last two trimesters of pregnancy and the risk of small-for-gestational-age (SGA) newborns.

Study Design: Case-control study within the Quebec Pregnancy Registry.

Setting: Province of Quebec, Canada.

Study population: Analyses were done on prospectively collected data of 63338 pregnant women that met eligibility criteria for the study (8192 cases and 55146 controls).

Methods: Unconditional logistic regression models were used to quantify the association between exposure to anti-infective drugs and the risk of SGA.

Main outcome measures: A case of SGA was defined as a pregnancy resulting in a baby's weigh adjusted for gestational age and gender <10th percentile, according to the Canadian gender-specific reference curves. A control was defined as a pregnancy resulting in a baby's weight adjusted for gestational age and gender ≥10th percentile.

Results: Exposure to all combined anti-infective drugs was not associated with the risk of SGA (OR= 0.97, 95%CI: 0.91-1.04). Use of sulfamethoxazole/trimethoprim was associated with SGA (OR= 1.61, 95%CI: 1.16-2.23), whereas the use of urinary anti-infective drugs decreased the risk (OR= 0.80, 95%CI: 0.65-0.97).

Conclusions: Exposure to sulfamethoxazole/trimethoprim during the last two trimesters of pregnancy was associated with SGA. Further research is needed to address the use of other therapeutic alternatives in the management of infections that predispose to SGA infants in pregnant women with other risk factors for this condition.

5.4.2. INTRODUCTION

Intrauterine growth restriction (IUGR) is an important and often under-diagnosed condition during pregnancy that may cause important implications on the health of an infant and on his on-going health (1). Small-for-gestational-age (SGA) is often taken as a good proxy for IUGR. Although the definition is somewhat arbitrary, a common cut-off point for SGA is the 10th percentile of birth weight for gestational age and sex, based on the distribution in the standard population. This is the one most often used definition in published clinical studies dealing with risk factors for IUGR (2). SGA babies are at increased risk of long-term morbidity, including neurologic and behavior problems, delayed growth during childhood, short stature, hypertension, obesity, and type II diabetes in adulthood (3,4). The exact consequences of SGA on the subsequent development of these infants depend on the specific cause giving rise to the IUGR, its time of occurrence and the duration of the impairment (5). As the burden is so significant, the detection and management of risk factors are crucial (6). Among the putative risk factors for SGA, common maternal infections have been positively associated with a sub-optimal placental perfusion and a dysfunction of the placental microvascularity, which results in an inadequate maternal supply of oxygen and nutrients to the fetus and the consequent decreased ability of the fetus to use the supply (1,7,8).

The use of anti-infective drugs seems to be the natural choice to treat maternal infections, thus preventing SGA and other infection-related adverse pregnancy outcomes. Despite the very frequent usage of anti-infective drugs during pregnancy (9), there is still some controversy regarding the risks and benefits of such usage on the pregnant woman and her unborn child. Only a few classes of antimicrobial compounds have been shown to be fetus-safe when used during gestation, such as older beta-lactams. Furthermore, the

association between these drugs and the risk of SGA has not been extensively assessed. Some studies have tested the hypothesis that maternal exposure to some antibiotics, such as sulfonamides and tetracyclines, could cause adverse pregnancy outcomes that share a placenta-mediated pathway, as in the cases for IUGR (10). Since randomized trials on therapeutic harm are rarely ethical and practical during pregnancy, this issue would be better addressed by large population-based studies derived from evidence-based data. A better understanding of the possible role of maternal anti-infective drug usage on fetal growth could eventually lead to interventions such as the identification of an effective treatment for women at higher risk of having SGA newborns.

Therefore, the objective of this study was to determine the association between anti-infective exposure during the second or third trimester of pregnancy and the risk of SGA, according to the class and type of anti-infective used.

5.4.2. METHODS

5.4.2.1. Data sources

We used the Quebec Pregnancy Registry, built from the linkage of three administrative databases: the *Régie de l'assurance maladie du Québec* (RAMQ), Med-Echo, and the *Institut de la statistique du Québec* (ISQ).

RAMQ database provides information on medical services dispensed to all Quebec residents and on prescriptions filled for residents insured by Quebec's Public Drug Insurance Plan. This database prospectively provides collected data on filled prescriptions, physician-based diagnoses (International Classification of Diseases, ninth revision, ICD-9) (11),

therapeutic procedures, characteristics of the patient and health care providers, and the costs involved. The RAMQ covers the costs for medical services provided to all Quebec residents and the drug insurance plan insures approximately 50% of Quebec residents, which include persons of 65 years or older, welfare recipients and their children, and all workers and their families who do not have access to a private drug insurance program (12). Access to health care services between women covered for their medications by the RAMQ's drug plan and those covered by private drug plans is similar (13).

The Med-Echo database records acute care hospitalization data for all Quebec residents; it also records gestational age for planned abortions, miscarriages and deliveries. Gestational age is defined from the first day of the last menstrual period to the end of pregnancy, and confirmed by ultrasound around the 18th-20th week of gestation.

The ISQ administers the *Fichier des événements démographiques* that provides data on all births and deaths in Quebec. The following demographic information is included: for the mother (date of birth, age, marital status, mother-tongue, place of birth, area of residence, number of live births, number of deliveries), for the father (date of birth, age, mother-tongue, place of birth); and for the baby (gender, type of delivery, weight, gestational age, order in the family, date of birth).

The linkage between RAMQ and Med-Echo data was done using patients' *Numéro d'assurance maladie* [258], which is a unique identifier for all legal residents of Quebec. The mother-child linkage was possible using the unique identifier that links each baby born in Quebec to his/her mother in the RAMQ database. The linkage between the RAMQ and ISQ was done using the first name, family name and date of birth of both the mother and child.

The RAMQ and Med-Echo databases have often been used for epidemiological research leading to scientific articles published in peer-reviewed medical journals (14-16). Data recorded in the RAMQ medication database and in the Med-Echo database have been formally evaluated and found to be comprehensive and valid (17). Medical diagnoses and data recorded in the ISQ databases have also been evaluated and found to be valid and precise (18,19). The Registry has often been used to assess the risks and benefits of drug use during pregnancy (20,21).

This study was approved by the Sainte-Justine Hospital Ethics Committee and by the *Commission d'accès à l'information du Québec*, the provincial agency that grants authorization for the use of linked administrative databases.

5.4.2.2. Study Population

Within the Registry, women meeting the following eligibility criteria were included in this study: (1) have between 15 and 45 years of age on the date of entry in the Registry defined as the first day of pregnancy (the first day of last menstrual period); (2) to be continuously insured by the RAMQ drug plan for at least 12 months prior to the first day of gestation and during pregnancy; and (3) gave birth to a live born singleton. The end of the pregnancy was defined as the calendar date of the delivery. If a woman had more than one pregnancy between 1998 and 2003, the first pregnancy meeting eligibility criteria was considered for analysis.

5.4.2.3. Study Design and Outcome Definition

We conducted a case-control study. Three independent analyses were done: the first analysis assessed the risk of SGA for all combined anti-infective

drugs; the second assessed the risk of SGA for the classes of anti-infective drugs; and the third assessed the risk for individual types of anti-infective.

A case of SGA was defined as a pregnancy resulting with a baby's weigh adjusted for gestational age and gender <10th percentile, according to the Canadian gender-specific reference curves (22). A control was defined as a pregnancy resulting with a baby's weight adjusted for gestational age and gender ≥10th percentile. The index date was defined as the date of delivery.

5.4.2.4. Exposure to Anti-infective Drugs

In all analyses, the exposure to anti-infective drugs was treated dichotomously. The exposure window was the pregnancy's second (>14 to ≤ 26 weeks of gestational age) or third trimester (>26 weeks of gestational age). To be considered as exposed in a particular trimester, pregnant women had to have filled at least one prescription for an anti-infective drug in the corresponding trimester, or if the duration of a prescription overlapped the corresponding trimester.

For the first analysis, overall exposure to at least one anti-infective drug (all combined) was compared to no exposure (reference category). For the second analysis, anti-infective drugs were grouped in the following American Hospital Formulary Service (AHFS) classes: cephalosporins (AHFS 8:12:06), macrolides (AHFS 8:12:12), penicillins (AHFS 8:12:16), sulfonamides (AHFS 8:12:20), urinary anti-infectives (AHFS 8:36) and other antibacterials (AHFS 8:12:28). For the third analysis, data were analyzed for the following individual drugs: ampicillin, amoxicillin, azithromycin, ciprofloxacin, clindamycin, doxycycline, erythromycin, fluconazole, metronidazole, nitrofurantoin, and sulfamethoxazole/ trimethoprim (SXT).

5.4.2.5. Covariates

The following variables were considered as potential confounders of the association between exposure to anti-infective drugs and the risk of SGA, and were measured in the year before and during pregnancy: number of different types of medications used other than anti-infectives, number of different prescribers for all medications, number of visits to the physician, visits to the emergency department and/or hospitalizations, diabetes (ICD-9 codes 250-259, 271.4, 790.2 and the filling of at least one prescription for medications for diabetes, - AHFS codes 68:20.08, 68:20.20, 68:20.92), asthma (ICD-9 codes 493.0, 493.1, 493.9 and the filling of at least one prescription for any anti-asthmatic drugs), hypertension (ICD-9 codes 640-642 and the filling of at least one prescription for any antihypertensive drugs - AHFS class 24:08), infections (ICD-9 codes 001-136), respiratory tract infections (ICD-9 codes 460-466, 472-487), urinary tract and sexually transmitted infections (UT and STI) ICD-9 codes 590, 599-599.6), pelvic inflammatory disease (ICD-9 codes 614-616), pre-term rupture of membranes (ICD-9 codes 658), anemia (ICD-9 codes 280-285), periodontal disease (ICD-9 codes 521-525), renal disorders (ICD-9 codes 580-589), depression (ICD-9 codes 296, 309, 311), nutritional disorders (ICD-9 codes 260-269), and thyroid disorders (ICD-9 codes 240-246). Diagnosis for hypertension and diabetes covers the entire study period. Diagnostic codes related to renal disorders refer to acute renal conditions. Women counted for these variables during the last year before pregnancy are not likely to be the same women with a code for this variable during pregnancy. In addition, we determined the following socio-economic variables at the index date from the RAMQ/ISQ databases: maternal age, maternal place of residence (urban versus rural), maternal RAMQ drug plan status (adherent versus welfare recipient) and calendar year of pregnancy.

5.4.2.6. Statistical Analysis

Descriptive statistics, Student t-tests and Chi-square test were used to compare cases and controls. Univariate and multivariate unconditional logistic regression models were built, adjusting for important confounders and proxy variables for socioeconomic, health services utilization and co-morbidities. Consistency of the model was evaluated by Hosmer-Lemeshow goodness of fit test. Sensitivity analysis was done using a cut-off point of <3rd percentile of birth weight for gestational age and sex, as definition for SGA. The association between anti-infective exposure and the risk of SGA was quantified by means of adjusted odds ratios (OR) along with 95% confidence intervals (95% CI). SAS version 9.1 (SAS Institute Inc. North Caroline, USA) was used to conduct analyses.

5.4.3. RESULTS

5.4.3.1. Characteristics of the Study Population

A total of 63 338 pregnant women within the registry met the eligibility criteria and were included in this study. The mean age of the cohort was 27.1 years (standard deviation: 5.6 years), 35% of women were welfare recipients and 80% were living in an urban area on the index date. The mean gestational age at delivery was 39.1 weeks for cases (median: 40 weeks, standard deviation: 1.7) and 38.8 weeks for controls (median: 39 weeks, standard deviation: 2.1). The prevalence of SGA in our study population was 13% (n= 8192 cases). Cases were more likely to be welfare recipients at the index date compared to controls (OR= 1.38, 95% CI: 1.31-1.45) (Table 1).

5.4.3.2. Exposure to Anti-infectives and the Risk of SGA

We found that anti-infective drugs used during the second or third trimester of pregnancy were higher in cases (20.1%) compared to controls (18.4%). Our data showed that exposure to anti-infective drugs (all combined) during this period was not associated with SGA (OR= 0.97, 95%CI: 0.91-1.04) (Table 1).

5.4.3.3. Classes and Types of Anti-infective and the Risk of SGA

Exposure to sulfonamides during the second or third trimester of pregnancy was significantly associated with SGA, when analyses were done using no exposure to sulfonamides as the reference group (OR= 1.66, 95%CI: 1.20-2.30, Table 2), and when the reference group was formed by women exposed to penicillins (OR= 1.91, 95%CI: 1.23-2.95, Table 3). SXT was the individual sulfonamide drug associated with SGA (OR= 1.61, 95%CI: 1.16-2.23, Table 4)

The use of urinary anti-infectives during the same period decreased the frequency of SGA (OR= 0.80, 95%CI: 0.65-0.97, Table 2). Nitrofurantoin seems to be the responsible for this effect (OR= 0.80, 95%CI: 0.66-0.98, Table 4). Amoxicillin was another individual drug associated with a decreased frequency of SGA (OR =0.92, 95%CI: 0.85-0.99, Table 4).

There was no qualitative difference when the analyses were done using a cut-off point of <3rd percentile of birth weight for gestational age and sex, as definition for SGA.

5.4.4. DISCUSSION

The prevalence of SGA in our study population (13%) was higher than the one previously reported for the Canadian population (7.8%) (23). This can be due to the fact that our population is formed by women with a lower socio-economic status, which is a known risk factor for SGA (6). Furthermore, SGA is a relative measure and varies according to the standard used for calculation. There is still controversy as to what is the optimal method to assess newborn infant size in identifying SGA babies (24-26). The standard used for this study is the population-based Canadian reference for birth weight for gestational age (22).

Our results showed that in multivariate adjusted models, exposure to sulfonamides during the second or third trimester of pregnancy increases the probability of having a SGA newborn. These drugs are the first-line agent for the treatment of urinary tract infections among women allergic to penicillins (27). SXT is a folic acid antagonist that inhibits deoxyribonucleic acid synthesis by interfering with the production of folic acid. This combination is highly specific for bacterial DNA (28). However, recent evidence suggests that there is an association between exposure to SXT and adverse pregnancy outcomes, such as congenital malformations and placenta-mediated events like preeclampsia (10,29). In one of these studies, exposure to folic acid antagonists, for which SXT was the most prevalent, was associated with an increased risk of fetal growth restriction and fetal death (10). Although some methodological flaws in this study, the authors put their findings in perspective with a very strong biological rational: a placental microvascular disease may arise from a maternal folate-homocysteine metabolic defect caused by an exposure to these drugs. In the absence of confounding by indication, this can explain how SXT is associated with the development of the events that lead to SGA newborns. Other possible related factors are the

well documented SXT gastrointestinal adverse effects (nausea, vomiting, diarrhea and stomatitis) that could play a synergic role in preventing the fetus from receiving essential micronutrients from the mother (28).

Given the scarcity of sulfonamides exposure in our study population, it is unlikely that the population attributable risk for SGA due to such exposure is high enough to justify the SXT suspension from clinical practice. However, our findings bring attention to unsuspicious non-antibiotic properties of old and well known anti-infective drugs and the clinical implications of these properties. In fact, there is increasing evidence that some other anti-infectives, may show different biological actions in the modulation of the inflammatory pathway, apoptosis inhibition, regulation of bone metabolism and angiogenesis (30). Further research is needed to address this issue.

Nitrofurantoin and amoxicillin were associated with a reduction in the risk of SGA, although the clinical significance of the amoxicillin risk reduction is questionable. Nitrofurantoin is one of the oldest urinary anti-infective drugs available and it can be safely used by pregnant woman in any given trimester (29). The choice of SXT, nitrofurantoin or other drug as appropriate regimens for the management of urinary tract infections, is based upon the results from susceptibility testing (27). Nitrofurantoin can be an efficient candidate in the treatment of urinary tract infections in women with other SGA-related risk factors. Nevertheless, increasing nitrofurantoin resistance complicates the choice of empiric regimens.

To our knowledge, this is the first population-based study assessing the association between SGA and the use of anti-infective drugs in a large population of pregnant women. Furthermore, it has the largest sample size of all studies that addressed IUGR related outcomes. We were able to adjust for a large number of potential variables and predictors related to anti-infective

use and the risk of SGA. The assessments of exposures in studies using administrative databases offer the advantage of not being influenced by recall bias. We were also able to get accurate information on several classes and types of anti-infectives according to prescriptions.

This study had some limitations inherent to the use of administrative databases. We were unable to measure some risk factors for SGA such as smoking, illicit substances, alcohol and caffeine intake. Data on maternal height and weight are missing in the Quebec Pregnancy Registry. Indeed, these variables are associated with SGA. In the other hand, it is not clear if maternal height and weight are independently associated with anti-infective drugs use during gestation. However, residual confounding can be present. The dispensing of a prescription does not mean that a patient actually took the medication or was completely compliant with treatment. Nevertheless, the provincial drug plan requires that the beneficiary pay a portion of the costs of the prescription medications. This increases the likelihood that filled prescriptions are in fact consumed.

Multiple testing could partially explain some of our findings. Data were not available for pregnant women who did not use the public healthcare system. Given that Quebec's health insurance plan is free, we do not believe that this would confound our results, but rather affect the generalizability of some findings that may be more strongly associated with socio-demographic factors that could act as an effect modifier (13). Similarly, data are not available for anti-infective exposure in more severe hospital infections nor for over-the-counter drugs. However, all systemic anti-infective drugs available in Quebec are dispended by a pharmacist under the filling of a prescription, so this can reduce the probability of bias.

5.4.5. CONCLUSION

Exposure to sulfonamides and SXT during the last two trimesters of pregnancy was associated with an increased frequency of SGA. Use of nitrofurantoin and amoxicillin decreased the risk. Physicians should consider the use of other therapeutic alternatives to sulfonamides in the management of infections that predispose to SGA children in pregnant women with other risk factors for this condition.

5.4.6. REFERENCES

1. Brodsky D, Christou H. Current concepts in intrauterine growth restriction. J Intensive Care Med 2004; 19(6):307-19.

2. Gardosi J, Francis A. Adverse pregnancy outcome and association with small for gestational age birthweight by customized and population-based percentiles. Am J Obstet Gynecol 2009; 201(1):28.

3. Lundgren EM, Tuvemo T. Effects of being born small for gestational age on long-term intellectual performance. Best Pract Res Clin Endocrinol Metab 2008; 22(3):477-88.

4. Saenger P, Czernichow P, Hughes I, Reiter EO. Small for gestational age: short stature and beyond. Endocr Rev 2007; 28(2):219-51.

5. Valero De BJ, Soriano T, Albaladejo R, Juarranz M, Calle ME, Martinez D, et al. Risk factors for low birth weight: a review. Eur J Obstet Gynecol Reprod Biol 2004; 10;116(1):3-15.

6. Grivell R, Dodd J, Robinson J. The prevention and treatment of intrauterine growth restriction. Best Pract Res Clin Obstet Gynaecol 2009; 15.

7. Mazor-Dray E, Levy A, Schlaeffer F, Sheiner E. Maternal urinary tract infection: is it independently associated with adverse pregnancy outcome? J Matern Fetal Neonatal Med 2009; 22(2):124-8.

8. Germain M, Krohn MA, Hillier SL, Eschenbach DA. Genital flora in pregnancy and its association with intrauterine growth retardation. J Clin Microbiol 1994; 32(9):2162-8.

9. Santos F, Oraichi D, Berard A. Prevalence and predictors of anti-infective use during pregnancy. Pharmacoepidemiol Drug Saf 2010; 19:418-27.

10. Wen SW, Zhou J, Yang Q, Fraser W, Olatunbosun O, Walker M. Maternal exposure to folic acid antagonists and placenta-mediated adverse pregnancy outcomes. CMAJ. 2008; 179(12):1263-8.

11. World Health Organization. International Classification of Diseases. 1997.

12. Régie de l'assurance maladie du Québec: Statistiques annuelles. Goverment of Quebec. 1997.

13. Berard A, Lacasse A. Validity of perinatal pharmacoepidemiologic studies using data from the RAMQ administrative database. Can J Clin Pharmacol. 2009;16(2):e360-9.

14. Blais L, Desgagne A, LeLorier J. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and the risk of cancer: a nested case-control study. Arch Intern Med 2000; 14;160(15):2363-8.

15. Garbe E, LeLorier J, Boivin JF, Suissa S. Risk of ocular hypertension or open-angle glaucoma in elderly patients on oral glucocorticoids. Lancet 1997; 4;350(9083):979-82.

16. Avorn J, Monette J, Lacour A, Bohn RL, Monane M, Mogun H, et al. Persistence of use of lipid-lowering medications: a cross-national study. JAMA 1998; 13;279(18):1458-62.

17. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and

comprehensiveness of the prescription claims database in Quebec. J Clin Epidemiol 1995; 48(8):999-1009.

18. Vilain A, Otis S, Forget A, Blais L. Agreement between administrative databases and medical charts for pregnancy-related variables among asthmatic women. Pharmacoepidemiol Drug Saf 2008; 17(4):345-53.

19. Levy AR, Mayo NE, Grimard G. Rates of transcervical and pertrochanteric hip fractures in the province of Quebec, Canada, 1981-1992. Am J Epidemiol 1995; 15, 142(4):428-36.

20. Ramos E, Oraichi D, Rey E, Blais L, Berard A. Prevalence and predictors of antidepressant use in a cohort of pregnant women. BJOG 2007; 114(9):1055-64.

21. Berard A, Azoulay L, Koren G, Blais L, Perreault S, Oraichi D. Isotretinoin, pregnancies, abortions and birth defects: a population-based perspective. Br J Clin Pharmacol 2007; 63(2):196-205.

22. Kramer MS, Platt RW, Wen SW, Joseph KS, Allen A, Abrahamowicz M, et al. A new and improved population-based Canadian reference for birth weight for gestational age. Pediatrics 2001; 108(2):E35.

23. Public Health Agency of Canada. Canadian Perinatal Health Report 2008. Ottawa: Ministry of Health; 2008.

24. Zhang X, Platt RW, Cnattingius S, Joseph KS, Kramer MS. The use of customised versus population-based birthweight standards in predicting perinatal mortality. BJOG 2007; 114(4):474-7.

25. Hutcheon JA, Zhang X, Cnattingius S, Kramer MS, Platt RW. Customised birthweight percentiles: does adjusting for maternal characteristics matter? BJOG 2008;115(11):1397-404.

26. Groom KM, Poppe KK, North RA, McCowan LM. Small-for-gestational-age infants classified by customized or population birthweight centiles: impact of gestational age at delivery. Am J Obstet Gynecol 2007; 197(3):239-5.

27. Smaill F, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. Cochrane Database Syst Rev 2007;(2):CD000490.

28. Libecco JA, Powell KR. Trimethoprim/sulfamethoxazole: clinical update. Pediatr Rev 2004; 25(11):375-80.

29. Guidelines. Antimicrobial Therapy - A Concise Canadian Guide 2007. Montreal: Prism; 2007.

30. Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. J Am Acad Dermatol 2006; 542:258-65.

Table 1. Exposure to anti-infective drugs during pregnancy and the risk of SGA and characteristics of the study population*

Variables	Cases (n, %) *(n=8192) (13%)*	Controls (n, %) *(n=55146) (87%)*	Crude OR *(95% CI)*	Adjusted OR *(95% CI)*
Anti-infective Drug use				
Anti-infective use during the second and/or the third trimesters of pregnancy				
No	6540 (79.8)	44982 (81.5)	1.00 (reference)	1.00 (reference)
Yes	1652 (20.1)	10164 (18.4)	1.11 (1.05-1.18)	0.97 (0.91-1.04)
Maternal characteristics at the index date				
Maternal age (mean, SD)	26.9 (5.8)	27.3 (5.5)	0.98 (0.98-0.99)	0.99 (0.99-1.00)
Gestational age (mean, SD)	39.1 (1.7)	38.8 (2.1)	**	**
Place of birth				
Rural	1924 (23.5)	12924 (23.4)	1.00 (reference)	1.00 (reference)
Urban	6268 (76.5)	42222 (76.6)	0.99 (0.94-1.05)	0.96 (0.90-1.01)
RAMQ Insurance Status				
Adherents	4907 (61.7)	36950 (69.7)	1.00 (reference)	1.00 (reference)
Welfare recipients	3045 (38.3)	16075 (30.3)	1.42 (1.36-1.49)	1.38 (1.31-1.45)

Health Status and medication use before pregnancy				
Number of different medications used				
0-2	5688 (69.4)	40549 (73.5)	1.00 (reference)	1.00 (reference)
3-5	1848 (22.5)	11157 (20.2)	1.18 (1.11-1.24)	1.06 (0.99-1.14)
≥ 6	656 (8.0)	3440 (6.2)	1.36 (1.24-1.48)	1.03 (0.92-1.16)
Number of different prescribers before pregnancy				
0-2	5691 (69.5)	40188 (72.9)	1.00 (reference)	1.00 (reference)
≥ 3	2501 (30.5)	14958 (27.1)	1.18 (1.12-1.24)	0.97 (0.90-1.05)
Emergency department visit/hospitalization				
No	6909 (84.3)	47215 (85.6)	1.00 (reference)	1.00 (reference)
Yes	1283 (15.7)	7931 (14.4)	1.10 (1.03-1.17)	1.00 (0.94-1.08)
Physician visits before pregnancy				
0-2	2499 (30.5)	17789 (32.2)	1.00 (reference)	1.00 (reference)
3-5	1901 (23.2)	13564 (24.6)	0.99 (0.93-1.06)	0.96 (0.90-1.03)
≥6	3792 (46.3)	23793 (43.1)	1.13 (1.07-1.12)	0.98 (0.92-1.06)
Comorbidities				
Infections	982 (11.9)	6009 (10.9)	1.11 (1.04-1.19)	1.03 (0.95-1.11)
Respiratory tract infections	1965 (23.9)	13041 (23.6)	1.02 (0.96-1.07)	0.95 (0.89-1.00)
Urinary tract and sexually transmitted infections	564 (6.8)	3276 (5.9)	1.17 (1.06-1.28)	1.06 (0.96-1.17)

Pelvic inflammatory disease	914 (11.1)	5571 (10.1)	1.12 (1.04-1.20)	1.04 (0.96-1.12)
Diseases of female genital tract	1709 (20.8)	10629 (19.2)	1.10 (1.04-1.16)	1.01 (0.95-1.08)
Asthma	1189 (14.5)	6840 (12.4)	1.20 (1.12-1.28)	1.04 (0.97-1.12)
Diabetes***	538 (6.5)	3866 (7.0)	0.93 (0.85-1.02)	0.80 (0.72-0.88)
Hypertension***	719 (8.8)	3502 (6.3)	1.42 (1.30-1.54)	1.35 (1.24-1.48)
Anemia	123 (1.5)	776 (1.4)	1.07 (0.88-1.29)	0.95 (0.78-1.16)
Periodontal disease	38 (0.4)	157 (0.2)	1.63 (1.14-2.33)	1.55 (1.07-2.22)
Renal disorders	20 (0.2)	79 (0.1)	1.71 (1.05-2.8)	1.19 (0.70-2.02)
Depression	426 (5.2)	2472 (4.5)	1.17 (1.05-1.23)	0.96 (0.86-1.08)
Nutritional disorders	6 (0.07)	30 (0.05)	1.34 (0.56-3.23)	1.35 (0.55-3.33)
Thyroid disorders	202 (2.5)	1350 (2.45)	1.00 (0.86-1.17)	0.94 (0.80-1.11)
Health Status and medication use during pregnancy				
Number of different medications used				
0-2	6589 (80.4)	46375 (84.1)	1.00 (reference)	1.00 (reference)
3-5	1230 (15.0)	7078 (12.8)	1.22 (1.14-1.30)	1.05 (0.97-1.14)
≥ 6	373 (4.5)	1693 (3.0)	1.55 (1.38-1.74)	1.22 (1.05-1.41)
Number of different prescribers during pregnancy				
0-2	6715 (82.0)	47145 (85.5)	1.00 (reference)	1.00 (reference)
≥ 3	1477 (18.0)	8001 (14.5)	1.30 (1.22-1.37)	1.05 (0.97-1.15)

Emergency department visit/hospitalization				
No	1517 (18.5)	5592 (10.1)	1.00 (reference)	1.00 (reference)
Yes	6675 (81.5)	49554 (89.9)	0.50 (0.46-0.52)	0.48 (0.45-0.51)
Physician visits during pregnancy				
0-2	117 (1.4)	865 (1.5)	1.00 (reference)	1.00 (reference)
3-5	287 (3.5)	1824 (3.3)	1.16 (0.92-1.46)	1.15 (0.90-1.46)
≥6	7788 (95.0)	52457 (95.1)	1.10 (0.90-1.33)	1.16 (0.94-1.43)
Comorbidities				
Infections	913 (11.1)	5965 (10.8)	1.03 (0.96-1.11)	0.99 (0.92-1.08)
Respiratory tract infections	1269 (15.5)	8235 (14.9)	1.04 (0.97-1.11)	0.96 (0.90-1.03)
Urinary tract and sexually transmitted infections	2261 (27.6)	14482 (26.2)	1.07 (1.01-1.12)	1.06 (1.00-1.12)
Pelvic inflammatory disease	616 (7.5)	4125 (7.5)	1.00 (0.92-1.09)	0.96 (0.87-1.05)
Diseases of female genital tract	1702 (20.8)	10491 (19.0)	1.11 (1.05-1.18)	1.10 (1.03-1.16)
Asthma	1225 (14.9)	6555 (11.9)	1.30 (1.22-1.39)	1.14 (1.06-1.23)
Diabetes***	538 (6.6)	3866 (7.0)	0.93 (0.85-1.02)	0.80 (0.72-0.88)
Hypertension***	719 (8.8)	3502 (6.3)	1.42 (1.30-1.54)	1.36 (1.24-1.48)
Anemia	172 (2.1)	964 (1.7)	1.20 (1.02-1.42)	1.17 (0.98-1.38)
Periodontal disease	21 (0.3)	64 (0.12)	2.21 (1.35-3.62)	1.97 (1.19-3.26)
Renal disorders	30 (0.4)	90 (0.16)	2.25 (1.48-3.40)	1.70 (1.09-2.67)
Depression	207 (2.5)	1036 (1.9)	1.35 (1.16-1.57)	1.17 (0.99-1.38)

Nutritional disorders	10 (0.12)	36 (0.07)	1.87 (0.92-3.77)	1.79 (0.87-3.70)
Thyroid disorders	188 (2.3)	1124 (2.0)	1.13 (0.96-1.32)	1.16 (0.97-1.38)
Pprom	1147 (14.0)	8043 (14.6)	0.95 (0.89-1.02)	1.04 (0.97-1.12)
Cesarian section	483 (5.9)	4127 (7.5)	0.77 (0.70-0.85)	0.82 (0.74-0.91)

[*] Analysis adjusted for calendar year of pregnancy.

[**] Given that SGA is a composite measure that takes into account gestational age at delivery, there is no need to adjust for GA at delivery in the analysis.

[***] Diagnosis covering the entire study period.

Table 2. Exposure to anti-infective classes during pregnancy and the risk of SGA*

	Cases (n, %) *(n=8192) (13%)*	**Controls (n, %)** *(n=55146) (87%)*	**Crude OR** *(95% CI)*	**Adjusted OR** *(95% CI)*
Anti-infective drugs use by pharmacological class – 2nd or 3rd trimester				
		Cephalosporins		
No	8012 (97.8)	54178 (98.2)	1.00 (reference)	1.00 (reference)
Yes	180 (2.2)	968 (1.7)	1.26 (1.07-1.47)	1.09 (0.92-1.30)
		Macrolides		
No	7902 (96.5)	53626 (97.2)	1.00 (reference)	1.00 (reference)
Yes	290 (3.5)	1520 (2.8)	1.30 (1.14-1.47)	1.09 (0.95-1.24)
		Penicillins		
No	7085 (86.5)	48060 (87.1)	1.00 (reference)	1.00 (reference)
Yes	1107 (13.5)	7086 (12.9)	1.06 (0.99-1.13)	0.94 (0.87-1.01)
		Sulfonamides		
No	8141 (99.4)	54978 (99.7)	1.00 (reference)	1.00 (reference)
Yes	51 (0.6)	168 (0.3)	2.05 (1.50-2.80)	1.66 (1.20-2.30)
		Urinary anti-infectives		
No	8074 (98.5)	54293 (98.4)	1.00 (reference)	1.00 (reference)
Yes	118 (1.5)	853 (1.6)	0.93 (0.76-1.13)	0.80 (0.65-0.97)
		Others		
No	8126 (99.2)	54769 (99.3)	1.00 (reference)	1.00 (reference)
Yes	66 (0.8)	377 (0.7)	1.18 (0.90-1.50)	1.02 (0.78-1.33)

* Adjusted for all others variables present in Table 1 and calendar year of pregnancy.

Table 3. Exposure to anti-infective classes during pregnancy and the risk of SGA (reference group: women exposed to penicillins)*

	Cases (n, %) *(n=8192) (13%)*	**Controls (n, %)** *(n=55146) (87%)*	**Crude OR** *(95% CI)*	**Adjusted OR** *(95% CI)*
Class of anti-infective drug				
Cephalosporins	88 (1.07)	530 (0.96)	1.10 (0.86-1.39)	1.10 (0.86-1.39)
Macrolides	200 (2.4)	1065 (1.9)	1.24 (1.05-1.46)	1.17 (0.99-1.38)
Penicillins	933 (11.4)	6178 (11.2)	1.00 (reference)	1.00 (reference)
Sulfonamides	28 (0.34)	92 (0.17)	2.01 (1.31-3.09)	1.91 (1.23-2.95)
Urinary anti-infectives	67 (0.8)	527 (0.96)	0.84 (0.64-1.09)	0.82 (0.63-1.07)
Others	42 (0.5)	244 (0.4)	1.14 (0.81-1.59)	1.10 (0.79-1.55)

* Adjusted for all variables present in Table 1 and calendar year of pregnancy.

Table 4. Exposure to individual anti-infective drugs during pregnancy and the risk of SGA (reference group: women with no exposure to each drug)*

	Cases (n, %) *(n=8192) (13%)*	**Controls (n, %)** *(n=55146) (87%)*	**Crude OR** *(95% CI)*	**Adjusted OR** *(95% CI)*
Effect of individual drugs				
Ampicillin	16 (0.20)	101 (0.18)	1.07 (0.63-1.81)	0.96 (0.57-1.65)
Amoxicillin	890 (10.8)	5827 (10.5)	1.03 (0.95-1.11)	0.92 (0.85-0.99)
Azithromycin	56 (0.68)	354 (0.64)	1.06 (0.80-1.41)	0.87 (0.65-1.17)
Ciprofloxacin	20 (0.24)	60 (0.11)	2.24 (1.35-3.72)	1.56 (0.92-2.64)
Clindamicin	55 (0.67)	299 (0.54)	1.24 (0.92-1.65)	1.06 (0.80-1.43)
Doxyciclin	5 (0.06)	14 (0.03)	2.40 (0.86-6.68)	1.13 (0.40-3.19)
Erythromycin	239 (2.9)	1204 (2.2)	1.34 (1.17-1.55)	1.15 (0.99-1.33)
Fluconazole	25 (0.3)	95 (0.2)	1.77 (1.14-2.75)	1.34 (0.85-2.12)
Metronidazole	47 (0.6)	276 (0.5)	1.14 (0.84-1.56)	0.98 (0.72-1.35)
Nitrofurantoin	118 (1.4)	853 (1.5)	0.93 (0.76-1.12)	0.80 (0.66-0.98)
Sulfamethoxazole/ trimethoprim	49 (0.6)	165 (0.3)	2.00 (1.45-2.76)	1.61 (1.16-2.23)

* Adjusted for all variables present in Table 1 and calendar year of pregnancy.

5.5. RISKS AND BENEFITS OF THE USE OF METRONIDAZOLE DURING PREGNANCY: A REVIEW OF THE EVIDENCE

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5.5.1. ABSTRACT

Background: Metronidazole is an anti-infective drug used against infections, such as tricomoniasis and bacterial vaginosis. Given that these conditions are known risk factors for preterm birth, this agent is potentially useful during pregnancy. However, available data on the risk of metronidazole during gestation is contradictory and controversial.

Objectives: To present an overview of the evidence concerning the association between the use of metronidazole during pregnancy and the risk of preterm delivery and birth defects.

Methods: We systematically searched PUBMED and EMBASE databases for etiologic studies with data on human subjects that examined the association between gestational exposure to metronidazole and the risk of preterm birth or birth defects. Combinations of the following MeSH terms were used: “metronidazole” or “prematurity” or “preterm birth” or “congenital malformations” or “birth defects” or “anomalies” or “pregnancy” or “antibiotics” or “bacterial vaginosis” or “trichomoniasis”. All relevant articles, published in English or French between 1964 and 2010, were reviewed. If authors did not report the odds ratio (OR) for preterm birth or birth defects, crude ORs and 95% confidence intervals (CI) were calculated.

Results: 17 studies that investigated the association between exposure to oral metronidazole during pregnancy and the risk of preterm birth were included. Twelve of these studies were randomized clinical trials. We also retrieved 13 studies that investigated the association between exposure and the risk of birth defects. Ten of these were cohort studies; one was a case-control study and two were meta-analysis.

Conclusions: Treatment with metronidazole is effective against bacterial vaginosis and tricomoniasis during pregnancy, and offers no teratogen risk for babies of exposed women. Benefit of metronidazole in the reduction of preterm birth rates was demonstrated only for the combination of this agent with other antibiotics. More evidence is needed on the risk of birth defects, when metronidazole is used in association.

5.5.2. INTRODUCTION

Metronidazole is an anti-infective drug used particularly against anaerobic infections. It is widely prescribed for the treatment of tricomoniasis and bacterial vaginosis in women of childbearing age. Given that these conditions are known risk factors for adverse pregnancy outcomes, such as preterm rupture of membranes and preterm birth, metronidazole is a potentially useful agent during pregnancy (1). However, this drug is able to cross the placenta throughout gestation and evidence from animal studies suggests that, when used in association with miconazole, metronidazole is a teratogen (2-4). Data on the risk of this agent during pregnancy is contradictory and hence, the use of metronidazole during pregnancy has been controversial (5).

There is also lack of consensus on the use of metronidazole to prevent preterm birth. Metronidazole taken between 24th and 29th weeks of gestation for the treatment of trichonomiaisis is associated with an increased risk of preterm birth (6). In another study, treatment with metronidazole did not reduce early preterm birth in pregnant women at higher risk and without abnormal vaginal flora (7). However, other studies showed that the drug effectively reduces preterm birth rates when used in association with other agents for the treatment of pregnant women with bacterial vaginosis (8). In addition, women that had preterm birth in their previous pregnancy saw their risk of subsequent preterm birth reduced after treatment with metronidazole (9). Current clinical practice guidelines recommend oral treatment with metronidazole during pregnancy if the objective of therapy is to eradicate bacterial vaginosis and tricomoniasis (10).

We present an overview of the evidence available on the association between the use of metronidazole during gestation and the risk of preterm delivery and birth defects.

5.5.3. METHODS

We systematically searched MEDLINE (accessed via PubMed) and EMBASE databases for human studies published between 1964 and 2010. Combinations of the following MeSH terms were used: “metronidazole” or “prematurity” or “preterm birth” or “congenital malformations” or “birth defects” or “anomalies” or “pregnancy” as well as “antibiotics” or “bacterial vaginosis” or “trichomoniasis”. Additional references were identified from the reference lists of retrieved articles. All relevant articles, including prospective and retrospective studies, reviews and meta-analysis, published in English or French that examined the association between gestational exposure to metronidazole and the risk of adverse pregnancy outcomes (having data on preterm birth or birth defects) were reviewed. Only etiologic studies with clinical relevant definition of exposure were considered (exposure during the last two trimesters of pregnancy for studies evaluating preterm birth and exposure during the first trimester for birth defects). The initial selection criteria were broad enough to ensure that as many studies as possible were assessed for review. Case series and studies that reported exposure to other routes of administration (topical or intravenous) without data on oral exposure were excluded.

For each selected study, the following information was retrieved: first author’s name, year of publication, study population, study design, exposure definition, data source, results including p-values, and relative risks (RR) or odds ratios (OR) when provided.

When authors did not report the OR for preterm birth or birth defects, we calculated crude ORs and 95% confidence intervals (CI) from the available data in order to compare study results and interpret data. We also calculated the prevalence of preterm birth and birth defects, for papers where these data

were not reported. Analyses were performed using the SAS System for Windows Version 9.1.3 (SAS Institute Inc, North Carolina, USA).

5.5.4. RESULTS

5.5.4.1. Studies on gestational exposure to metronidazole and the risk of preterm birth

Our search strategy retrieved a total of 908 references, from which 225 were initially considered for inclusion. After an exhaustive assessment of their titles and abstracts, 187 documents were rejected, leaving 38 for full text evaluation. 17 studies that investigated the association between exposure to oral metronidazole during pregnancy and the risk of preterm birth met inclusion criteria and were included for analysis. The majority of these studies (12) were randomized clinical trials (RCT). Three were cohort studies and two were systematic reviews or meta-analysis. Delivery before 37 weeks of gestation was the primary outcome for the majority of these studies. Exposure to metronidazole alone was the main exposure definition in 10 studies, whereas the rest of the articles assessed exposure to metronidazole in association with other antibiotics. Characteristics of reviewed studies are presented in table 1 and 2.

5.5.4.2. Studies on gestational exposure to metronidazole and the risk of birth defects

Our search strategy retrieved a total of 131 references, from which 98 were initially considered for inclusion. After an exhaustive assessment of their titles and abstracts, 52 documents were rejected, leaving 46 for full text evaluation. Finally, we retrieved 13 studies that investigated the association between exposure to metronidazole during pregnancy and the risk of birth defects. Ten

were cohort studies; one was a case-control study and two were meta-analysis. Any birth defect was the primary outcome for the majority of these studies, whereas some articles assessed only major defects. Exposure to metronidazole (alone or in combination) during the first trimester of pregnancy was the main exposure in all the studies. Some articles also assessed exposure during the third trimester of pregnancy. Characteristics of reviewed articles are presented in table 3.

5.5.5. DISCUSSION

5.5.5.1. Gestational exposure to metronidazole alone and the risk of preterm birth

In 1994, Morales et al. used a placebo-controlled RCT to determine if treatment of bacterial vaginosis with metronidazole was effective in reducing preterm birth rates in patients with preterm delivery in their previous pregnancy (9). The authors concluded that treatment (250 mg of metronidazole three times a day for 7 days) was effective in reducing preterm births (calculated crude OR: 0.27, 95%CI: 0.10-0.76). Nevertheless, at that time it was not clear whether pregnant women in their first gestation would benefit with treatment.

To clarify this question, in 1997 McDonald et al. randomised 879 pregnant women with a diagnosis of bacterial vaginosis at 19 weeks of gestation to receive oral metronidazole (400 mg) or placebo twice daily for two days (11). Intention-to-treat analysis showed no difference between metronidazole and placebo groups in overall preterm birth rates [(31/429 - 7.2% of cases among exposed) versus (32/428 - 7.5% of cases among unexposed)] or spontaneous preterm birth (4.7% versus 5.6%). In a subgroup of women with previous history of preterm birth, the authors were able to verify the same

protective effect reported earlier by Morales et al. (9): exposure to metronidazole reduced the risk of spontaneous preterm birth by 85% when compared to placebo (adjusted OR: 0.14, 95% CI: 0.01-0.84).

However, results from a population-based observational study conducted by Sorensen et al. in 1999 suggested a lack of effect of metronidazole in reducing rates of delivery before 37 weeks of gestation (OR: 0.80, 95%CI: 0.35-1.83). However, information on previous preterm births and indication for use were lacking in their dataset (12).

This issue was further addressed in 2000 by Carey et al. who also did not find any evidence of a protective effect of metronidazole in the reduction of preterm births in a general obstetrical population (RR: 1.0, 95%CI: 0.8–1.2) (13). In this RCT, women with previous preterm birth history did not benefit with therapy (RR: 1.3, 95%CI: 0.8–2.0). Similar results were obtained by the same team in 2001: treatment of pregnant women asymptomatic for bacterial vaginosis was ineffective in preventing preterm delivery, and may even had increased the risk when compared to placebo (RR: 1.8, 95%CI: 1.2–2.7) (6). In the same year, Goldenberg et al. published another RCT conducted in which pregnant women with a positive test result for cervicovaginal fetal fibronectin and bacterial vaginosis had lower rates of preterm delivery after exposure to metronidazole (14). However, despite findings suggesting a protective effect, authors stated that it is unknown whether any antibiotic regimen reduced preterm birth associated with an intrauterine infection.

At that point of the evidence, metronidazole treatment of infections that predispose to preterm birth only showed to be effective for pregnant women with a previous inflammatory process caused by a chronic infection and hence, treatment of asymptomatic women would not be useful. This could partially explain the results of Morales et al. (9) and McDonald et al. (11). In

these studies, the subjects with a history of preterm birth suffered from a chronic bacterial processes, and this could be responsible for their findings of lower rates of preterm birth after exposure to metronidazole. In 2005, Odendaal et al. conducted a RCT in which metronidazole did not reduce the prevalence of preterm labour in pregnant women with a previous history of preterm birth and active bacterial vaginosis infection (15). Furthermore, results of a larger RCT conducted by Shennan et al. (7), the PREMET study, did not corroborate the previous results of Goldenberg et al. (14). The PREMET study showed that metronidazole did not reduce early preterm birth in high-risk pregnant women selected by history of previous preterm birth and positive test result for cervicovaginal fetal fibronectin (RR: 1.9, 95%CI: 0.72–5.09). Rate of delivery before 37 weeks of gestation was increased after exposure to metronidazole (RR: 1.6, 95% CI: 1.05–2.4). In addition, a systematic review published in 2005 by Okun et al. found no evidence to support the use of antibiotic treatment for bacterial vaginosis or Trichomonas vaginalis in order to reduce the risk of preterm birth or its associated morbidities (16).

Based on the results of their meta-analyis, Morency and Bujold concluded that the use of metronidazole should be avoided during the second trimester of pregnancy (17). It is not clear why metronidazole used alone may increase the risk of early delivery but it is possible that the eradication of normal bacterial vaginal flora caused by this agent allows growth of harmful organisms, leading to ascending infection, stimulation of the inflammatory process and early delivery.

Even if a recent observational study conducted in 2009 by Mann et al. showed that treatment with oral metronidazole was associated with a decrease in the risk of preterm birth (RR = 0.69, 95%CI 0.50-0.95) (18), most

of the available evidence from prior RCTs indicate that metronidazole used alone is not effective in reducing preterm delivery (Figure 1).

5.5.5.2. Gestational exposure to metronidazole in association with other antibiotics and the risk of preterm birth

In spite of the controversy regarding the use of metronidazole alone for the treatment of infections that predispose to preterm birth, the benefits of the association of this agent with other antibiotics was demonstrated during the decade of 1990. In 1994, Norman et al. conducted a multicentre RCT with 81 pregnant women, and showed the efficacy of the association ampicillin plus metronidazole for the prevention of preterm birth in women with intact membranes (OR: 0.34, 95%CI: 0.13-0.94) (19). Similar results were found when the association was done with erythromycin (RCT conducted in 1995 by Hauth et al. with 624 patients (8)), ampicillin (RCT conducted in 1997 by Svare et al. with 112 patients, calculated OR: 0,41, 95%CI: 0.19-0.87 (20)), tinidazole and secnidazole (retrospective cohort conducted in 2005 by Camargo et al., calculated OR: 0.13, 95%CI: 0.05-0.38 (21)), and cephalexin (RCT conducted in 2005 by Sen et al. with 224 patients, OR: 0.60, 95%CI: 0.19-1.88 (22)), although in this study, results were not statistically significant.

Despite these findings, which seemed to indicate a clear benefit of treating bacterial vaginosis with metronidazole in association with other antibiotics, a large systematic review conducted by Okun et al. in 2005 concluded that there is no evidence to support antibiotic treatment of pregnant women with bacterial vaginosis if the objective is to reduce preterm birth (RR: 0.93, 95%CI: 0.70-1.22) (16). The authors however, did not assess the benefits of metronidazole in association with other antibiotics.

In 2003, Andrews et al. conducted an RCT that showed no benefit of treatment with metronidazole in association with erythromycin during the second trimester of gestation for asymptomatic women with a positive cervical or vaginal fetal fibronectin test (OR: 1.17, 95% CI: 0.80-1.70) (23). Similar results were found when metronidazole and azithromycin were used during the interpregnancy interval in non-pregnant women with a previous preterm birth (RR: 1.12, 95%CI: 0.76-1.64) (24). However, this trial was designed to evaluate the potential benefit of administering an antibiotic intervention to non-pregnant women before conception in an effort to reduce preterm delivery in the subsequent pregnancy; hence exposure did not take place during pregnancy.

The lack of efficacy of treatment with metronidazole associated with other agents showed by some studies raised the question if there is an adverse interaction between the antibiotics and the physiological process inducing preterm birth, which could be responsible for the increase in the risk. To investigate this effect, in 2007 Tita et al. analyzed the existence of an interaction between the endometrial bacterial micro-flora and antibiotics administered to prevent preterm birth (25). Using subgroup analysis of a previous trial (24), the authors demonstrated that when present in the vaginal environment, specific microorganisms interact with metronidazole and azithromycin to increase the rate of preterm birth (RR: 1.45, 95%CI: 1.08-1.94 when Gardnerella vaginalis was present, and RR: 1.36, 95%CI: 1.03-1.79, when Gram-negative rods were present).

Even if the reviewed evidence shows a potential benefit for the use of metronidazole in association with other antibiotics (Figure 2), caution should be exercised in prescribing metronidazole with other drugs to pregnant women solely for the purpose of preventing preterm birth.

5.5.5.3. Gestational exposure to metronidazole and the risk of birth defects

One of the early studies that examined whether exposure to metronidazole during pregnancy is associated with any birth defects was a retrospective cohort conducted by Scott-Gray et al. in 1964 (26). The authors analyzed outcomes of 183 pregnancies and exposure during the first and third trimesters of gestation. There was no case of birth defects in children of women exposed during the first trimester of pregnancy. A noteworthy finding of this study was a case of spontaneous abortion after exposure to the drug. Similar results were found in a cohort of 190 pregnant women followed by Robinson and Mirchandani in 1965 (27), and in a cohort study of 32 subjects conducted by Rodin and Hass in 1966 (28). Again, no cases of birth defects were detected after exposure during the first trimester of gestation. The work of Rodin and Hass (28) was the only study to have no children with birth defects in the comparison group. Peterson et al. in 1966 was unable to verify an association between exposure and birth defects (prospective cohort of 128 pregnant women) (29). In all these studies, the primary outcome was any birth defects.

The first studies that pointed to a possible link between exposure to metronidazole and the risk of birth defects appeared in the decade of 1970. Any major congenital malformation was the outcome of interest in a prospective cohort study with data on 50282 pregnancies conducted by Heinonen et al. in 1977 (30). The authors found a non-statistically significant association between exposure during the first trimester of pregnancy and the risk of birth defects (RR: 2.15, 95%CI: 0.75-6.13). Four cases of birth defects were detected among 31 children of exposed women. The rate of such birth defects in the control group was 6.4%. Morgan conducted a similar cohort study with 350 subjects two years later and did not find any increased risk of

malformation after exposure during the first trimester (RR: 1.14, 95%CI: 0.23-5.52) (31). Both studies lacked statistical power and the number of exposed subjects was small.

In 1987, Rosa et al. conducted a large retrospective cohort study of 104339 subjects, using data issued from computerized Medicaid records (32). The authors assessed prescriptions filled during the first trimester of pregnancy for several antimicrobial compounds. 63 cases of birth defects were counted among 1083 women exposed to metronidazole during the first trimester of pregnancy, compared to 6501 cases in 103 256 non-exposed women. No association was found (OR: 0.92, 95%CI: 0.71-1.19).

Piper at al. published a cohort study using data from Tennessee Medicaid enrollment files (33). Two cohorts of pregnant women who delivered live-born or stillborn infants were identified. The exposed cohort consisted of 1387 women who filled a prescription for metronidazole between 30 days before and 120 days after the onset of their last normal menstrual period. The unexposed cohort consisted of 1387 comparable women who did not fill a prescription for metronidazole during the same time. Pregnancy outcomes were similar for the exposed and unexposed cohort subjects. There was no excess of any birth defect occurrence in the offspring of exposed women (RR: 1.2, 95%CI: 0.9-1.6).

Using data from previous reports (26-32), Burtin et al. published a meta-analysis where they concluded that metronidazole does not appear to be associated with an increased risk of birth defects (34). The overall weighted OR for exposure versus no exposure during the first trimester calculated was 0.93 (95% CI: 0.73-1.18).

A subsequent meta-analysis published by Caro-Paton et al. pooled findings from previous studies (30-33) and added results from a case-control study conducted with data of 41862 subjects (35). The authors found no association between metronidazole exposure during the first trimester of pregnancy and the risk of birth defects (OR = 1.08, 95% CI: 0.90-1.29), corroborating the findings of the meta-analysis of Burtin et al (34).

The use and refinement of data from administrative databases in the decade of 1990s and in the early 2000's, was reflected by the publication of several case-control and retrospective cohort studies conducted with large number of subjects. These advancements increased statistical power to addressing rare issues such as birth defects (36). In one of such study, Czeizel and Rockenbauer conducted a case-control analysis using the Hungarian Case-Control Surveillance of Congenital Abnormalities dataset (37). The control group consisted of 30 663 pregnant women who had healthy babies. The case group consisted of 17 300 pregnant women. Prevalence of exposure to metronidazole was 3.4% and 3.8% in the control and case groups, respectively. Authors concluded that treatment with oral metronidazole during the first trimester of pregnancy was not associated with congenital abnormalities (OR= 1.14, 95% CI: 0.89-1.46). However, since data on exposure was obtained by questionnaire-oriented interview, results could be subject to recall bias.

In order to avoid recall bias, Sorensen et al. conducted a retrospective cohort study using prescription filled data issued from the linkage of three Danish health administrative databases (12). Data on exposure was obtained from the pharmacoepidemiological prescription database from the North-Jutland, whereas data from birth defects was obtained from the Danish medical birth registry. The authors analyzed data of 138 prescriptions for metronidazole obtained by 124 women. The association between exposure during the first

trimester and the risk of birth defects was assessed by a case-cohort design. The prevalence of birth defects was 2.4% in the exposed group compared to 5.2% in the control group, and no increase in risk was found (OR: 0.44, 95%CI: 0.11-1.81).

In 2001, Diav-Citrin et al. prospectively followed 228 women exposed to metronidazole during pregnancy, 86.2% of whom with first-trimester exposure (38). Pregnancy outcome was compared with that of women who were counseled during the same period for non-teratogenic exposure. There was no difference in the rate of major malformations between the groups (3 cases of birth defects among 190 women exposed (1.6%) compared to 8 cases among 575 unexposed (1.4%). The rate of major malformations did not differ between the groups even after including elective terminations of pregnancy due to prenatally diagnosed malformations (RR: 1.13, 95%CI: 0.30-4.23).

The results from the studies discussed above do not indicate that metronidazole used alone poses a teratogenic threat for humans after exposure during the first trimester of pregnancy (Figure 3). However, a recent study demonstrated that rodents exposed in utero to metronidazole plus miconazole had a significant increment in the incidence of axial skeletal defects (26.6% of the fetus presented defective skeletogenesis after metronidazole - miconazole co-exposure) (4). In adition, a population-based case-control study conducted in 2005, warned for the possible correlation between use of topical metronidazole in combination with other anti-infectives and human birth defects (39). The analysis of cases and their matched controls indicated an association between second and third month exposure to vaginal metronidazole plus miconazole and the risk of poly-syndactyly (adjusted OR: 6.0, 95% CI: 2.4–15.2). Although recall bias and confounding by indication were present in this study, in a previous work (40) the same authors reported an association between vaginal metronidazole isolated

treatment during the second and third months of gestation and congenital hydrocephalus (OR: 10.7, 95% CI: 1.1–104.5). Their results however, were based only on five cases.

5.5.6. CONCLUSION

Evidence indicates that oral treatment with metronidazole is effective against bacterial vaginosis and tricomoniasis during pregnancy, and offers no teratogen risk for the babies of exposed women. Benefit of metronidazole in the reduction of preterm birth was demonstrated for the use of this agent in association with other antibiotics. However, more evidence is needed to assess the risk of birth defects, when metronidazole is used in combination with other drugs. Therefore, once organogenesis is complete, associations of metronidazole with other antibiotics should be considered for treating infections that predispose to preterm birth, when other equally effective therapeutic options are not available or are contraindicated.

5.5.7. REFERENCES

1. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet 2008;371:75-84.

2. Giknis ML, Damjanov I. The transplacental effects of ethanol and metronidazole in Swiss Webster mice. Toxicol.Lett. 1983;19:37-42.

3. Ivanov I. [Effect of the preparation trichomonacid on pregnancy in experimental animals]. Akush.Ginekol.(Sofiia) 1969;8:241-44.

4. Tiboni GM, Marotta F, Castigliego AP. Teratogenic effects in mouse fetuses subjected to the concurrent in utero exposure to miconazole and metronidazole. Reprod.Toxicol. 2008;26:254-61.

5. Einarson A, Ho E, Koren G. Can we use metronidazole during pregnancy and breastfeeding? Putting an end to the controversy. Can.Fam.Physician 2000;46:1053-54.

6. Klebanoff MA, Carey JC, Hauth JC, Hillier SL, Nugent RP, Thom EA et al. Failure of metronidazole to prevent preterm delivery among pregnant women with asymptomatic Trichomonas vaginalis infection. N.Engl.J.Med. 2001;345:487-93.

7. Shennan A, Crawshaw S, Briley A, Hawken J, Seed P, Jones G et al. A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervicovaginal fetal fibronectin: the PREMET Study. BJOG. 2006;113:65-74.

8. Hauth JC, Goldenberg RL, Andrews WW, DuBard MB, Copper RL. Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis. N.Engl.J Med. 1995;333:1732-36.

9. Morales WJ, Schorr S, Albritton J. Effect of metronidazole in patients with preterm birth in preceding pregnancy and bacterial vaginosis: a placebo-controlled, double-blind study. Am.J Obstet.Gynecol. 1994;171:345-47.

10. Workowski, K.A. and S. Berman, Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep, 2010. 59(RR-12): p. 1-110.

11. McDonald HM, O'Loughlin JA, Vigneswaran R, Jolley PT, Harvey JA, Bof A et al. Impact of metronidazole therapy on preterm birth in women with bacterial vaginosis flora (Gardnerella vaginalis): a randomised, placebo controlled trial. Br.J Obstet.Gynaecol. 1997;104:1391-97.

12. Sorensen HT, Larsen H, Jensen ES, Thulstrup AM, Schonheyder HC, Nielsen GL et al. Safety of metronidazole during pregnancy: a cohort study of risk of congenital abnormalities, preterm delivery and low birth weight in 124 women. J Antimicrob.Chemother. 1999;44:854-56.

13. Carey JC, Klebanoff MA, Hauth JC, Hillier SL, Thom EA, Ernest JM et al. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. N.Engl.J Med. 2000;342:534-40.

14. Goldenberg RL, Klebanoff M, Carey JC, Macpherson C. Metronidazole treatment of women with a positive fetal fibronectin test result. Am.J Obstet.Gynecol. 2001;185:485-86.

15. Odendaal HJ, Popov I, Schoeman J, Smith M, Grove D. Preterm labour--is bacterial vaginosis involved? S.Afr.Med.J. 2002;92:231-34.

16. Okun N, Gronau KA, Hannah ME. Antibiotics for bacterial vaginosis or Trichomonas vaginalis in pregnancy: a systematic review. Obstet.Gynecol. 2005;105:857-68.

17. Morency AM, Bujold E. The effect of second-trimester antibiotic therapy on the rate of preterm birth. J.Obstet.Gynaecol.Can. 2007;29:35-44.

18. Mann JR, McDermott S, Zhou L, Barnes TL, Hardin J. Treatment of trichomoniasis in pregnancy and preterm birth: an observational study. J.Womens Health (Larchmt.) 2009;18:493-97.

19. Norman K, Pattinson RC, de SJ, de JP, Moller G, Kirsten G. Ampicillin and metronidazole treatment in preterm labour: a multicentre, randomised controlled trial. Br.J Obstet.Gynaecol. 1994;101:404-08.

20. Svare J, Langhoff-Roos J, Andersen LF, Kryger-Baggesen N, Borch-Christensen H, Heisterberg L et al. Ampicillin-metronidazole treatment in idiopathic preterm labour: a randomised controlled multicentre trial. Br.J Obstet.Gynaecol. 1997;104:892-97.

21. Camargo RP, Simoes JA, Cecatti JG, Alves VM, Faro S. Impact of treatment for bacterial vaginosis on prematurity among Brazilian pregnant women: a retrospective cohort study. Sao Paulo Med.J 2005;123:108-12.

22. Sen A, Mahalanabis D, Mukhopadhyay S, Chakrabarty K, Singh AK, Bisai S et al. Routine use of antimicrobials by pregnant Indian women does not

improve birth outcome: a randomized controlled trial. J Health Popul.Nutr. 2005;23:236-44.

23. Andrews WW, Sibai BM, Thom EA, Dudley D, Ernest JM, McNellis D et al. Randomized clinical trial of metronidazole plus erythromycin to prevent spontaneous preterm delivery in fetal fibronectin-positive women. Obstet.Gynecol. 2003;101:847-55.

24. Andrews WW, Goldenberg RL, Hauth JC, Cliver SP, Copper R, Conner M. Interconceptional antibiotics to prevent spontaneous preterm birth: a randomized clinical trial. Am.J Obstet.Gynecol. 2006;194:617-23.

25. Tita AT, Cliver SP, Goepfert AR, Conner M, Goldenberg RL, Hauth JC et al. Clinical trial of interconceptional antibiotics to prevent preterm birth: subgroup analyses and possible adverse antibiotic-microbial interaction. Am.J Obstet.Gynecol. 2007;197:367-6.

26. Scott-Gray M. Metronidazole in Obstetristics Practice. J Obstet.Gynaecol.Br.Commonw. 1964;71:82-85.

27. Robinson SC, Mirchandani G. Trichomonas vaginalis. V. Further observations on metronidazole (Flagyl) (including infant follow-up). Am.J Obstet.Gynecol. 1965;93:502-05.

28. Rodin P, Hass G. Metronidazole and pregnancy. Br.J Vener.Dis. 1966;42:210-12.

29. Peterson WF, Stauch JE, Ryder CD. Metronidazole in pregnancy. Am.J Obstet.Gynecol. 1966;94:243-49.

30. Heinonen OP SDSS. Birth defects and drugs in pregnancy. Littleton, Massachusetts: PSG Publishing, 1977:296-302.

31. Morgan I. Metronidazole treatment in pregnancy. Int.J Gynaecol.Obstet. 1978;15:501-02.

32. Rosa FW, Baum C, Shaw M. Pregnancy outcomes after first-trimester vaginitis drug therapy. Obstet.Gynecol. 1987;69:751-55.

33. Piper JM, Mitchel EF, Ray WA. Prenatal use of metronidazole and birth defects: no association. Obstet.Gynecol. 1993;82:348-52.

34. Burtin P, Taddio A, Ariburnu O, Einarson TR, Koren G. Safety of metronidazole in pregnancy: a meta-analysis. Am.J Obstet.Gynecol. 1995;172:525-29.

35. Caro-Paton T, Carvajal A, Martin dD, I, Martin-Arias LH, Alvarez RA, Rodriguez PE. Is metronidazole teratogenic? A meta-analysis. Br.J Clin.Pharmacol. 1997;44:179-82.

36. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. J.Clin.Epidemiol. 1995;48:999-1009.

37. Czeizel AE, Rockenbauer M. A population based case-control teratologic study of oral metronidazole treatment during pregnancy. Br.J Obstet.Gynaecol. 1998;105:322-27.

38. Diav-Citrin O, Shechtman S, Gotteiner T, Arnon J, Ornoy A. Pregnancy outcome after gestational exposure to metronidazole: a prospective controlled cohort study. Teratology 2001;63:186-92.

39. Kazy Z, Puho E, Czeizel AE. The possible association between the combination of vaginal metronidazole and miconazole treatment and poly-syndactyly Population-based case-control teratologic study. Reprod.Toxicol. 2005;20:89-94.

40. Kazy Z, Puho E, Czeizel AE. Teratogenic potential of vaginal metronidazole treatment during pregnancy. Eur.J Obstet.Gynecol.Reprod.Biol. 2005;123:174-78.

Table 1. Exposure to metronidazole and the risk of preterm birth.

Author	***Source population, country***	***Study Design***	***Data source***	***Exposure definition***	***Main outcome definition***	***Results***	***Odds Ratio or Relative Risk (95% CI)***
1. Morales et al., 1994	N=80 United States	Randomised controlled trial (double blinded, placebo controlled)	Orlando Regional Medical Center	250 mg of metronidazole three times a day for 7 days	Preterm birth in women with a previous history	Exposed: 44 Unexposed: 36 Cases among exposed: 8 (18%) Cases among unexposed: 16 (44.4%)	OR: 0.27 (0.10-0.76)*
2. McDonald et al., 1997	N=879 Australia	Randomised controlled trial (double blinded, placebo controlled)	Women's and Children's Hospital, North Adelaide	Exposure to oral metronidazole (400 mg) twice daily for two days	Spontaneous preterm birth less than 37 weeks of gestation	Exposed: 429 Unexposed: 428 Cases among exposed: 31 (7.2%) Cases among unexposed: 32 (7.5%)	OR: 0.14 (0.01-0.84)

Continuation of Table 1

3. Sorensen et al. 1999	N=13451 Denmark	Retrospective cohort	Danish Medical Birth Registry	Exposure 30 days before conception, during the first trimester and any time during pregnancy	Delivery before 37 weeks of gestation	Exposed: 124 Unexposed: 13327 Cases among exposed: 6 (5%) Cases among unexposed: 93 (6%)	OR: 0.80 (0.35-1.83)
4. Carey et al. 2000	N=1953 United States	Randomised controlled trial (placebo controlled)	National Institute of Child Health and Human Development	Two-dose regimen of 2000mg each in women with bacterial vaginosis and without trichomoniasis	Delivery before 37 weeks of gestation	Exposed: 966 Unexposed: 987 Cases among exposed: 116 (12%) Cases among unexposed: 121 (12.2%)	RR: 1.0 (0.8–1.2)

Continuation of Table 1

5. Goldenberg et al. 2001	N=89 United States	Randomised controlled trial (placebo controlled)	National Institute of Child Health and Human Development	Two-dose regimen of 2000mg each in women with bacterial vaginosis and a positive test result for cervicovaginal fetal fibronectin	Delivery before 37 weeks of gestation	Exposed: 48 Unexposed: 41 Cases among exposed: 4 (8.3%) Cases among unexposed: 6 (14.6%)	OR: 0.5 (0.13-1.92)*
6. Klebanoff et al. 2001	N=617 United States	Randomised controlled trial (placebo controlled)	National Institute of Child Health and Human Development	Two-dose regimen of 2000mg each in women with asymptomatic trichomoniasis	Delivery before 37 weeks of gestation	Exposed: 320 Unexposed:297 Cases among exposed: 60 (19%) Cases among unexposed: 32 (10.7%)	RR: 1.8 (1.2–2.7)

Continuation of Table 1

7. Odendaal et al. 2002	N=269 South Africa	Randomised controlled trial (placebo controlled)	Tygerberg Hospital	400 mg metronidazole, orally twice daily for 2 days	Delivery before 37 weeks	Exposed: 136 Unexposed: 133 Cases among exposed: 42 (30.8%) Cases among unexposed: 25 (18.8%)	OR: 1.93 (1.09-3.40)
8. Shennan et al. 2006	N=100 United Kingdom	Randomised placebo-controlled trial	Fourteen UK hospitals	Metronidazole 400-mg for seven days	Delivery before 37 weeks of gestation	Exposed: 53 Unexposed: 47 Cases among exposed: 18 (39%) Cases among unexposed: 33 (62%)	RR: 1.6 (1.05 - 2.4)

Continuation of Table 1

9. Morency and Bujold, 2007	N=2779 Canada	Meta-Analysis	PubMed, Medline, and Embase Databases	Exposure to oral metronidazole	Delivery prior to 37 weeks' gestation	Exposed: 2779 Unexposed: 2531 Cases among exposed: 464 (16.7%) Cases among unexposed: 359 (14.2%)	OR: 1.10 (0.95-1.29)
10. Mann et al. 2009	N=3579 United States	Retrospective cohort	Medicaid billing data and birth certificate records in South Carolina	Prescription for oral metronidazole	Delivery prior to 37 weeks' gestation	Exposed: 1436 Unexposed: 2143 Cases among exposed: 182 (12.7%) Cases among unexposed: 327 (15.3%)	HR: 0.69 (0.52-0.92)

Table 2. Exposure to metronidazole in association with other antibiotics and the risk of preterm birth.

Author	***Source population, country***	***Study Design***	***Data source***	***Exposure definition***	***Main outcome definition***	***Results***	***Odds Ratio or Relative Risk (95% Confidence Intervals)***
1. Norman et al. 1994	N=81 South Africa	Randomised controlled trial.	Tygerberg Hospital (University of Stellenbosch), Somerset Hospital (University of Cape Town) and Coronation Hospital (University of Witwatersrand, Johannesburg)	Ampicillin 1 g intravenously repeated six hourly thereafter for 24 h, followed by amoxicillin 500 mg orally eight hourly for five days; concurrent metronidazole 1 g suppository, then 400 mg orally eight hourly for five days.	Delivery within seven days of admission.	Exposed: 43 Unexposed: 38 Cases among exposed: 16 (37.2%) Cases among unexposed: 23 (60.5%)	OR: 0.34 (0.13-0.94)

Continuation of Table 2

2. Hauth et al. 1995	N=624 United States	Randomised controlled trial (double blinded, placebo controlled)	Public health clinics in Jefferson County, Alabama	Metronidazole (250 mg three times a day for 7 days) and erythromycin (333 mg three times a day for 14 days)	Rate of delivery before 37 weeks' gestation among women with and without bacterial vaginosis	Exposed:433 Unexposed: 191 Cases among exposed: 112 (26%) Cases among unexposed: 68 (36%)	RR: 1.1 (0.8–1.7) for all subjects RR: 1.6 (1.1–2.1) for subjects with bacterial vaginosis
3. Svare et al. 1997	N=112 Denmark	Randomised controlled trial (double blinded, placebo controlled)	Six obstetric departments in the Copenhagen area	Eight days intravenous and oral treatment with ampicillin and metronidazole	Rate of delivery before 37 weeks' gestation among	Exposed: 59 Unexposed: 51 Cases among exposed: 25 (42%) Cases among unexposed: 33 (65%)	OR: 0.41 (0.19-0.87)

Continuation of Table 2

4. Andrews et al. 2003	N=703 United States	Randomised controlled trial	Department of Obstetrics and Gynecology, Center for Research in Women's Health	Metronidazole (250 mg orally three times per day) and erythromycin (250 mg orally four times per day)	Delivery before 37 weeks' gestation after preterm labor or premature membrane rupture	Exposed: 347 Unexposed: 356 Cases among exposed: 50 (14.4%) Cases among unexposed: 44 (12.4%)	OR: 1.17 (0.80-1.70)
5. Camargo et al. 2005	N=205 Brazil	Retrospective cohort	Obstetric Service at the Universidade Estadual de Campinas	Metronidazole, 750 mg/day, orally for seven days; metronidazole, tinidazole or secnidazole, 2 g orally, single dose	Delivery before 37 weeks of gestation	Exposed: 134 Unexposed: 71 Cases among exposed: 5 (3.7%) Cases among unexposed: 16 (22.5)	OR: 0.13 (0.05-0.38)*

Continuation of Table 2

6. Okun et al. 2005	N=6052 Canada	Systematic review	Pre-Med, Medline, Embase and the Cochrane Library	Exposure to metronidazole	Delivery before 37 weeks of gestation	Exposed: 3146 Unexposed: 2906 Cases among exposed: 426 (13.5%) Cases among unexposed: 83 (13.17%)	OR: 0.93 (0.70-1.22)
7. Sen et al. 2005	N=224 India	Randomised controlled trial	Government hospital in Kolkata, India	Metronidazole 200 mg eight hourly for seven days and + cephalexin 500 mg capsules 12 hourly for five days.	Delivery before 37 weeks of gestation	Exposed: 112 Unexposed: 112 Cases among exposed: 9 (7.9%) Cases among unexposed: 12 (10.7%)	OR: 0.60 (0.19-1.88)*

Table 3. Exposure to metronidazole and the risk of birth defects.

Author	***Source population and country***	***Study Design***	***Data source***	***Exposure definition***	***Outcome definition***	***Results***	***Chi squared, Odds Ratio or Relative Risk or Other (95% CI)***
1. Scott-Gray, 1964	N=183 United Kingdom	Prospective cohort	Edinburgh Royal Hospital	Exposure during the first or third trimester of pregnancy with 200mg of metronidazole	Any birth defect	Exposed:79 Unexposed: 104 Cases among exposed: 0 (0%) Cases among unexposed: 4 (3.8%)	Chi squared: 1.57 p=0.21

Continuation of Table 3

2. Robinson and Mirchanda -ni, 1965	N=190 United States	Prospective cohort		Exposure during the first or third trimester of pregnancy	Any birth defect	Exposed:14 Unexposed: 196 Cases among exposed: 0 (0%) Cases among unexposed: 4 (2%)	Chi squared: 0.158 p=0.69
3. Rodin and Hass 1966	N=32 United Kingdom	Prospective cohort	Whitechap el Clinic – London Hospital	Exposure during the first trimester of pregnancy, 200mg of metronidazole, T.I.D, 1 week	Any birth defect	Exposed:13 Unexposed: 19 Cases among exposed: 0 (0%) Cases among unexposed: 0	No cases of birth defects

Continuation of Table 3

4. Peterson et al. 1966	N=128 United States	Prospective cohort		Exposure during the first or third trimester of pregnancy	Any birth defect	Exposed: 54 Unexposed: 74 Cases among exposed: 0 (0%) Cases among unexposed: 1 (1.35%)	Chi squared: 0.025 p=0.87
5. Heinonen et al. 1977	N=50282 United States	Prospective cohort		Exposure during the first of pregnancy	Major birth defects	Exposed: 31 Unexposed: 50251 Cases among exposed: 4 (13%) Cases among unexposed: 3244 (6.4%)	RR: 2.15 (0.75-6.13)

Continuation of Table 3

6. Morgan, 1978	N=350 United States	Retrospective cohort		Exposure during the first of pregnancy	Any birth defect	Exposed: 63 Unexposed: 287 Cases among exposed: 2 (3.2%) Cases among unexposed: 8 (2.8%)	RR: 1.14 (0.23-5.52)
7. Rosa et al. 1987	N=104339 United States	Retrospective cohort	Computerized Medicaid records	Exposure to miconazole, clotrimazole, nystatin, candicidin, aminacrine compounds, and metronidazole during the first trimester of pregnancy	Any birth defect	Exposed: 1083 Unexposed: 103256 Cases among exposed: 63 (5.8%) Cases among unexposed: 6501 (6.3%)	RR: 0.92 (0.8-1.6)

Continuation of Table 3

8. Piper et al. 1993	N=2774 United States	Retrospective cohort	Tennessee Medicaid files	Exposure during the first trimester of pregnancy	Major birth defects	Exposed: 1387 Unexposed: 1387 Cases among exposed: 96 (7%) Cases among unexposed: 80 (5.7%)	RR: 1.2 (0.9-1.6)
9. Burtin et al. 1993	N=104872 Canada	Meta-Analysis		Exposure during the first or third trimester of pregnancy	Any birth defect		OR: 0.93 (0.73-1.18)
10. Caro-Paton et al. 1997	N=199451 Spain	Meta-Analysis		Exposure during the first trimester of pregnancy	Any birth defect		OR=1.08 (0.90-1.29)

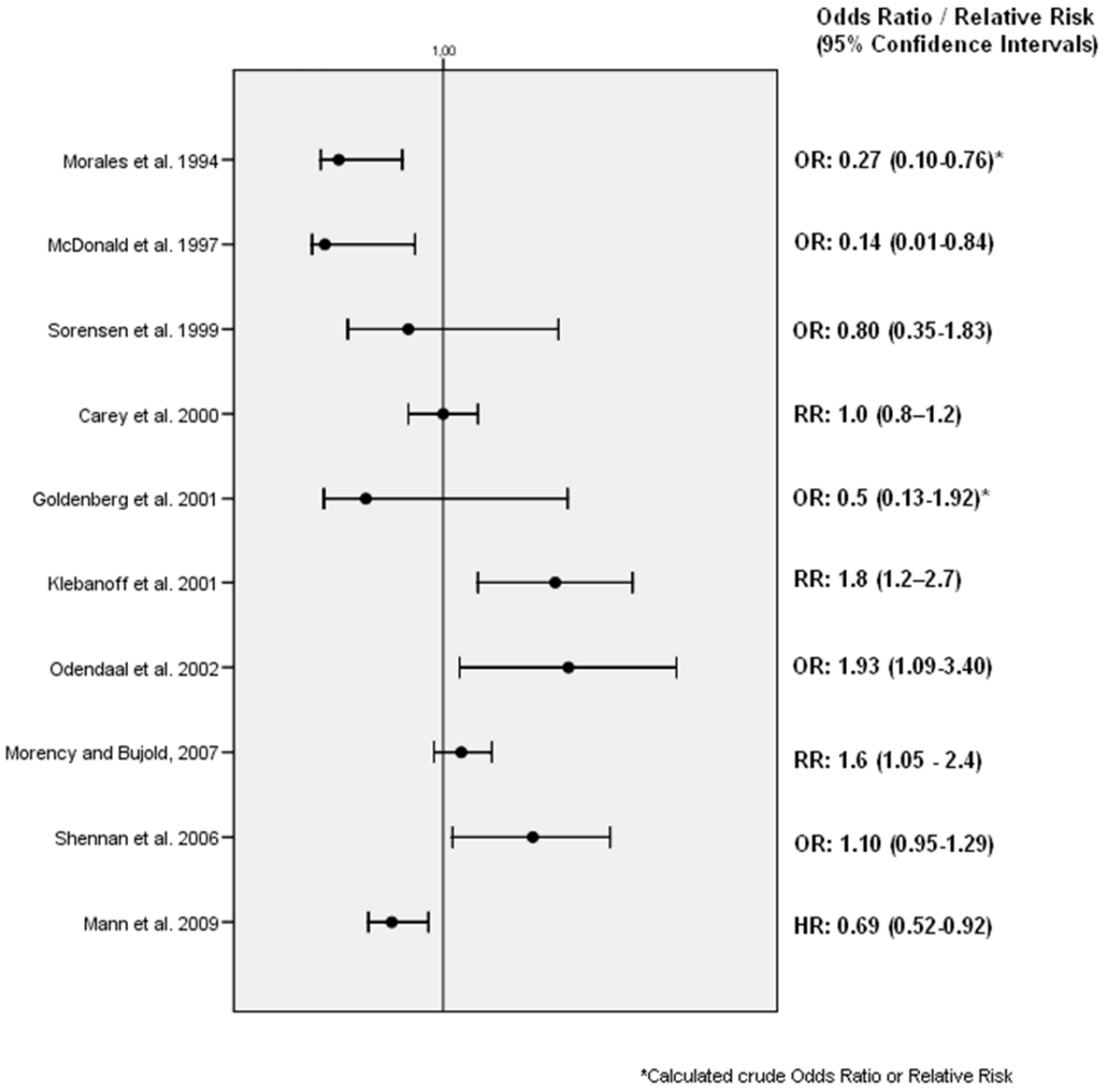
Continuation of Table 3

11. Czeizel and Rockenbauer, 1998	N=47963 Hungary	Case-control	Hungarian Surveillance of Congenital Abnormalities database	Exposure during the first trimester of pregnancy, 250mg of metronidazole	Major birth defects	Cases: 17300 Controls: 30663 Exposed cases: 665 (3.8%) Exposed controls: 1041 (3.4%)	OR: 1.14 (0.89-1.46)
12. Sorensen et al. 1999	N=13451 Denmark	Retrospective cohort	Danish Medical Birth Registry	Exposure 30 days before conception and during the first trimester of pregnancy	Any birth defect	Exposed: 124 Unexposed: 13327 Cases among exposed: 3 (2.4%) Cases among unexposed: 693 (5.2%)	OR: 0.44 (0.11-1.81)

Continuation of Table 3

13. Diav-Citrin et al., 2001	N= 791 Israel	Prospective cohort	Israeli Teratogen Information Service	Exposure during the first trimester of pregnancy	Major birth defects	Exposed: 205 Unexposed: 586 Cases among exposed: 3 (1.45%) Cases among unexposed: 8 (1.3%)	RR:1.13 (0.30–4.23)

Figure 1. Exposure to metronidazole and the risk of preterm birth.



*Calculated crude Odds Ratio or Relative Risk

Figure 2. Exposure to metronidazole in association with other antibiotics and the risk of preterm birth

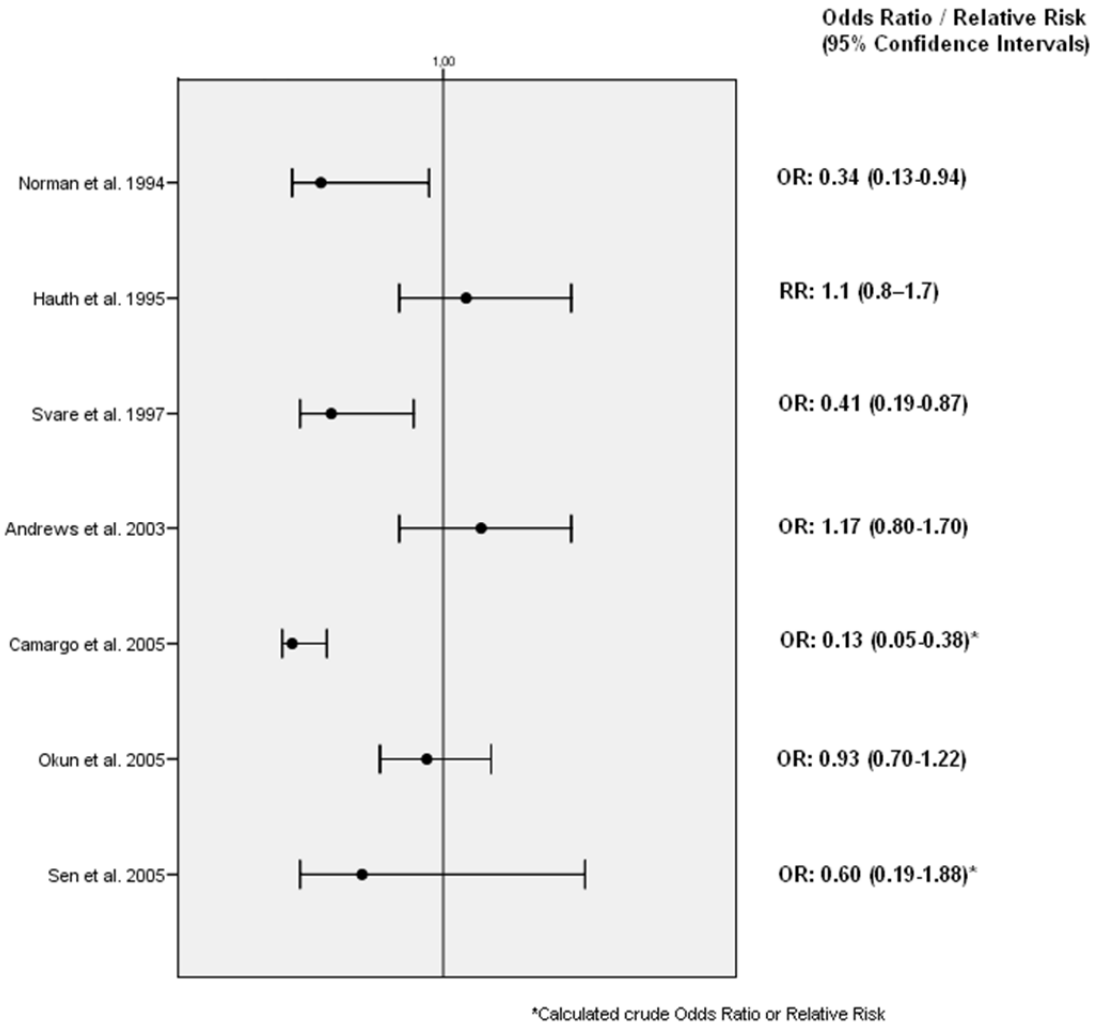
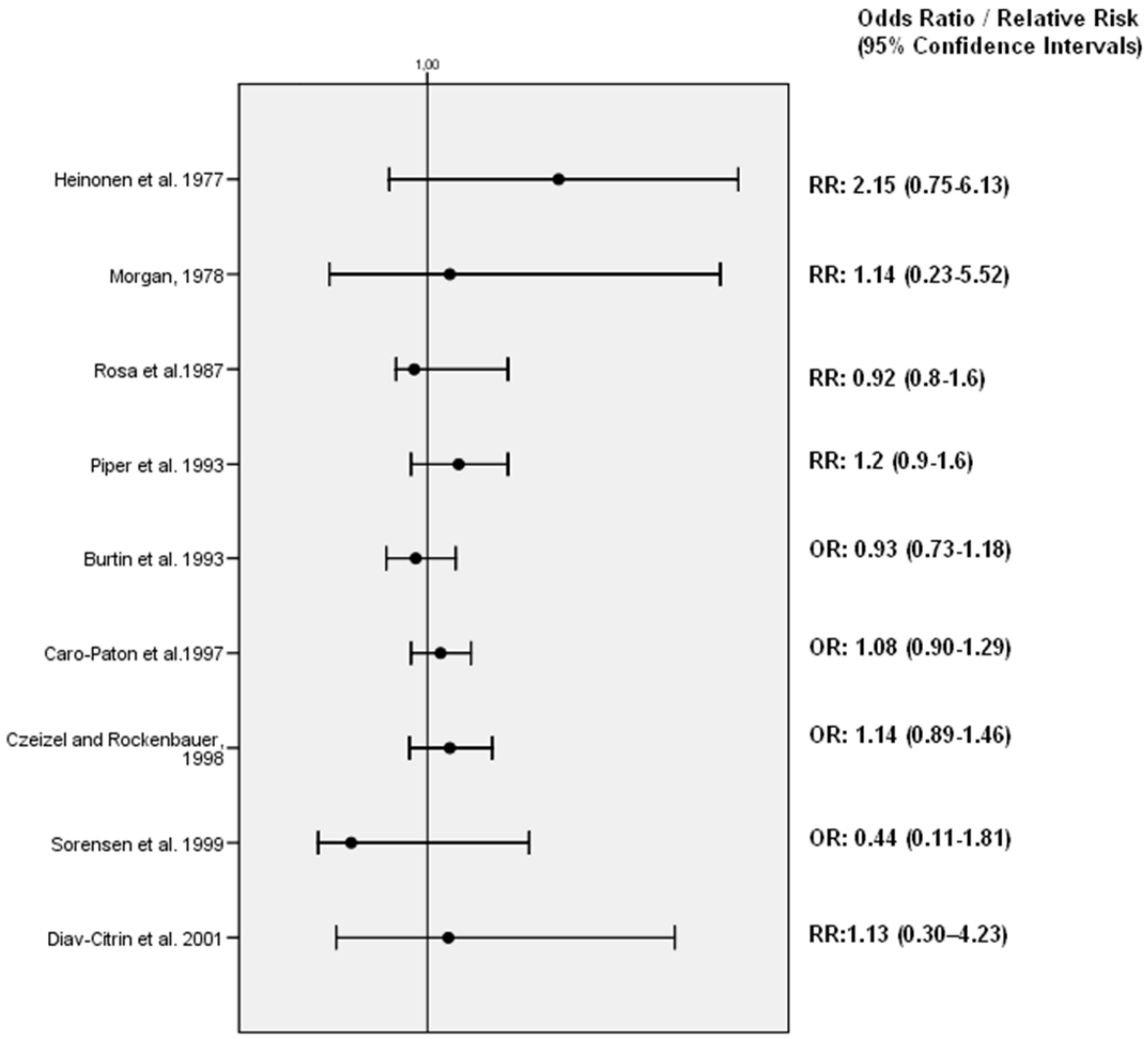


Figure 3. Exposure to metronidazole and the risk of birth defects.



Chapter 6
DISCUSSION

Considering the controversy regarding the use of anti-infective drugs during pregnancy, and the fact that part of this controversy is due to the methodological quality of the available evidence on the subject (see section 2.4 of this thesis), we conducted 4 large population-based studies to further investigate the risk of these drugs during gestation. In addition, we systematically reviewed the available evidence on the risk of metronidazole, which is the first line agent for the treatment of bacterial vaginosis (a condition itself associated to preterm birth).

Our main goal was to furnish additional evidence-based data on the risk of two placenta-mediated adverse outcomes (preterm birth and SGA) after exposure to anti-infectives drugs during critical periods of pregnancy. In addition, using data from health administrative databases, we aimed to overcome some of the methodological flaws that limited a reasonable interpretation of the results from previous published studies.

Studies 1 and 2 presented in this thesis determined to whom, for which indications, why and to which extent anti-infective drugs were prescribed during pregnancy. These studies also determined trends in use, and helped us to establish the research agenda for the design of study 3 and 4.

In Study 1, we found that 24.5% of pregnant women were exposed at least once to an anti-infective drug during gestation (15% of pregnant women were exposed at least once during the first trimester of pregnancy, 10% during the second or third trimester). The use of these drugs decreased once pregnancy

was diagnosed. Prevalence of use reached pre-pregnancy level after the end of gestation. This study also showed that, 66% of the anti-infective drugs used during the first trimester are considered safe – drugs that are not associated with adverse pregnancy outcomes, such as penicillins and macrolides. This number rises to 77% in the second, and to 86% in the third trimester of pregnancy. Predictors of use on the first day of gestation were factors related to lower socio-economic status and poor health conditions. Study 2 showed a decreasing trend in the overall use of anti-infective drugs during pregnancy from 1998 to 2002, and more specifically of broad-spectrum agents ($p \leq 0.05$ for trends). These findings corroborate the results published by other studies from different countries [2, 49, 54]. At the time Study 1 was published, it was the most complete study examining exhaustively, the prevalence, indications and trends of anti-infective drugs use during pregnancy, and the only one that had data on relevant predictors of use.

Findings of these studies indicate that physicians may be reluctant in prescribing anti-infective drugs once pregnancy is diagnosed. Furthermore, the decrease in the use of broad-spectrum antibiotics detected in Study 2 can be a direct consequence of a consensus among health care professionals to prescribe fewer anti-infective drugs in an effort to decrease resistance. Data from the Canadian Rx atlas indicates that there was a decrease in the inflation-adjusted per capita spending for oral antibiotics during the period comprised between 1997 and 2007 [265]. The same trend was observed in the age-standardized analysis and in all provinces. Given that the analyses were held with data issue of retail sales of prescriptions medicines sold in Canada, these results corroborate the conclusions of Study 2.

Study 1 showed that respiratory tract infections was the most prevalent infection diagnosed in the registry. Some physiologic changes that occur during pregnancy can predispose pregnant women to these infections

(increased minute ventilation, which is caused by increased respiratory center sensitivity and drive; a compensated respiratory alkalosis; and a low expiratory reserve volume). Furtheremore, immunological modifications in the number and function of T and B lymphocytes and hormonal alterations also may play a role [266]. Other indications for use of anti-infective drugs during pregnancy detected in Study 1 was urinary tract infections and sexually transmitted infections. Given that these conditions are known risk factors for some adverse pregnancy outcomes, these findings led us to investigate the independent risk of preterm birth and SGA associated with exposure to anti-infective drugs during pregnancy.

Study 3 demonstrated that exposure to all anti-infective drugs combined during the last two trimesters of pregnancy had a protective effect on the risk of preterm birth (adjusted OR=0.78 [95%CI: 0.70-0.88]. After adjustment for indication for use and several other covariates, the classes of anti-infectives responsible for this effect were penicillins (adjusted OR=0.65 [95%CI: 0.53-0.82] and macrolides (adjusted OR=0.65 [95%CI: 0.50-0.85]). Amoxicillin (adjusted OR=0.78 [95%CI: 0.70-0.87]) and erythromycin (adjusted OR=0.76 [95%CI: 0.61, 0.95]) both reduced the risk of preterm birth when the reference group were women with no exposure to such drugs, while metronidazole was associated with a 81% increase in the risk (adjusted OR=1.81 [95%CI: 1.30-2.54]).

These findings corroborate most of the available evidence on the use of such drugs to prevent preterm birth. A noteworthy finding of this study was the protective effect of azithromycin in women with a diagnosis of PROM (adjusted OR= 0.31, 95% CI: 0.10-0.93). This subgroup of women also had benefit from treatment with other agents, such as macrolides (adjusted OR=0.61, 95%CI: 0.41-0.90). This result indicates that azithromycin can be an effective alternative to erythromycin for the treatment of infections that

predispose to preterm birth. Furthermore, results from a recent meta-analysis indicated that azithromycin had similar effectiveness and less adverse effects compared with erythromycin or amoxicillin, when used in pregnant women [267]. Moreover, the widespread use of erythromycin has been responsible for an increase in bacterial resistance and consequent reduction in its efficacy.

Study 3 was the first study showing an association between the use of azithromycin and a decrease in the risk of preterm birth. In 2006, Sarkar et al. studied the effect of this drug on the prevalence of congenital malformations and preterm birth [127]. The authors concluded that azithromycin was not associated with a reduction in the risk of preterm birth. However, the results were based on a sample of only 123 pregnant women. Our results may encourage physicians in considering the use of this drug as an alternative in the management of infections that predispose to preterm birth. more research is needed to assess the risk of this drug with regards to other pregnancy outcomes.

We acknowledge the possibility that pregnant women exposed to anti-infective drugs to treat gestational infections could have had better clinical follow-up and access to health services, when compared to women that did not have anti-infective prescriptions. This factor could partially explain the protective effect of the use of anti-infective drugs among women with preterm birth.

Study 4 showed that exposure to anti-infective drugs all combined during the last two trimesters of pregnancy was not associated with the risk of SGA (adjusted OR= 0.97, 95%CI: 0.91-1.04). Class analysis revealed that exposure to sulfonamides was significantly associated with the risk of SGA (adjusted OR= 1.66, 95%CI: 1.20-2.30). SXT was the individual sulfonamide

drug associated to SGA (adjusted OR= 1.61, 95%CI: 1.16-2.23). The use of urinary anti-infectives decreased the risk of SGA (adjusted OR= 0.80, 95%CI: 0.65-0.97). Nitrofurantoin seemed to be responsible for this effect (adjusted OR= 0.80, 95%CI: 0.66-0.98). Amoxicillin was also associated with a decreased in the risk of SGA (adjusted OR =0.92, 95%CI: 0.85-0.99).

Wen et al. found same results in the only available study that assessed the risk of SGA after exposure to folic-acid antagonists, such as SXT [13]. However, the exposure time-window used to determine risk was a major limitation in this study. Indeed, a folic acid antagonist may have been dispensed up to 1 year before delivery. This means that a woman may have taken the medication up to 3 months before conception. It can be hard to justify that exposure before conception can have a lasting effect on the metabolism or the vascular integrity of a non-existent placenta [268]. Furthermore, in this study, the exposed group consisted of mothers who had received prescriptions for folic acid antagonists, all types combined. Although SXT is the most prevalent agent in the group, the estimates do not reflect the independent effect of this medication.

SXT is the first-line agent for the treatment of UTIs among women allergic to penicillins. Given that UTIs are known risk factors for SGA, it is possible that women treated with SXT had more severe infections than women treated with nitrofurantoin or with amoxicillin. Therefore, confounding by indication cannot be ruled out. However, our findings can be supported by a strong biological plausibility. SXT is a folic acid antagonist that inhibits deoxyribonucleic acid synthesis by interfering with the production of folic acid. A placental microvascular disease may arise from a maternal folate-homocysteine metabolic defect caused by exposure to SXT. In the absence of confounding by indication, this can explain how SXT is associated with the development of events that lead to SGA newborns.

Study 4 is the first population-based study assessing the association between the use of anti-infective drugs and the risk of SGA in a large population of pregnant women, using a biologically plausible exposure time-window. Its findings suggest that physicians should consider the use of other therapeutic alternatives to SXT in the management of UTIs in pregnant women with other risk factors for SGA. Moreover, this study adds evidence on unsuspicious biological properties of well known anti-infective drugs (such as SXT), and the clinical implications of these properties during gestation. Further research is needed to address this issue.

Finally, Study 5 is a systematic review of the evidence on the use of metronidazole during pregnancy with regards to the risk of birth defects and preterm birth. This study demonstrated that evidence from RCTs and observational studies indicates that oral treatment with metronidazole is effective against infections during pregnancy, and offers no teratogenic risk. However, with regards to prevention of preterm birth, benefits were only seen when metronidazole was used with other antibiotics. There is no evidence for the individual use of this drug to prevent preterm birth. These results corroborate the findings of Study 3, in which the use of oral metronidazole during the last two trimesters of pregnancy was associated with a 80% increase in the risk of preterm birth. More research is needed to determine the risk of birth defects, when metronidazole is used in combination with other drugs.

6.1. STRENGTHS AND LIMITATIONS

A detailed discussion of the strengths and limitations of this thesis is presented in each of the manuscripts described in Chapter 5. This section summarizes the advantages and weaknesses.

6.1.1. Strengths of the studies

6.1.1.1. Use of large populational, evidence-based data from health administrative databases and decreased chance of Selection bias

The first four studies presented in this thesis were conducted on a large sample of pregnant women obtained from the Quebec Pregnancy Registry. This registry is a longitudinal population-based pregnancy cohort established with the linkage of three health administrative databases from the province of Quebec. The use of these databases to measure associations between medication exposures during gestation and pregnancy outcomes presents many advantages over other data sources [269]. The Quebec Pregnancy Registry includes a wide variety of data, since it links several sources of health care information and includes a very large number of person-years of information. Data linkage is possible due to the high quality of the personal identifier in Quebec's administrative databases (the *Numero d'assurance maladie - NAM*), which allows correct linkage between databases.

Case-control studies can be highly vulnerable to selection bias, particularly in the selection of the control group. The essential purpose of the control group is to provide an estimate of exposure in the base population, the population from which the cases arise. Selection bias results if control selection is not neutral with respect to exposure. The population-based character of the Quebec Pregnancy Registry, allows the design of case-control studies nested

in pre-establihsed cohorts of pregnant women. Therefore, in Study 3 and 4, case and controls were selected from the same source population, which decreases the risk of selection bias.

Other advantages of using the Quebec Pregnancy Registry are the increased methodological flexibility, lower cost, and increased generalizability, given that data on the database reflects real clinical practice. The Quebec Pregnancy Registry has often been used to assess the risks and benefits of drug use during pregnancy [270-274].

6.1.1.2. Assessment of outcome: validity of data on SGA and gestational age

In study 3, preterm birth was defined as delivery before 37 completed weeks of gestation. This is the most used definition for preterm birth, which increases the comparability of our results [158]. Moreover, to ascertain SGA, we used a population-based Canadian reference for birth weight and gestational age, giving representative estimates for the study population [263]. In order to determine both outcomes, we used data on gestational age and birth weight, respectively.

One critical point when conducting etiologic studies during pregnancy is the accurate determination of the first day of gestation [275]. In the Quebec Pregnancy Registry, the pregnancies are first identified by a prenatal visit in the RAMQ database or by a therapeutic procedure related to pregnancy in RAMQ or Med-Echo files. Furthermore, Med-Echo database includes data on the length of gestation (defined from the first day of the last menstrual period to the end of pregnancy, validated by ultrasound). Med-Echo is the first administrative database to give exact gestational age at the end of pregnancy, which is a great advantage for studies on drug use during

gestation where timing of exposure is essential. Furtheremore, gestational age in ISQ database was validated against medical charts [260].

6.1.1.3. Study design and biological plausibility

Despite their status as gold standards in clinical research, randomized clinical trials may have the drawback of not reflecting real clinical practice. Furthermore, pregnant women are routinely excluded from clinical trials due to the concern that drugs could be risky for the fetus [276]. Observational studies are the only way to close the knowledge gap in pregnant women [264].

Studies 3 and 4 presented in this thesis are case-control studies conducted with data issued from the Quebec Pregnancy Registry. These studies are traditionally designed to investigate the risk of relatively rare outcomes (such as preterm birth and SGA), or to investigate multiple exposures (such as multiple classes and individual types of anti-infective drugs). Given that subjects are selected based on their outcome status, the case-control design permit increased power to detect events where baseline prevalence is different thatn zero, such as preterm birth and SGA. Furthermore, when compared to survival analysis and other study designs, the case-control design is particularly cost-effective with regards to computational time required to generate odds ratio that are close to the relative risk estimates [277].

In both studies, the exposure time-window chosen to evaluate the risk of preterm birth and SGA was the second or third trimester of gestation. Most of the risk factors for these two conditions take place during this critical period of pregnancy [72, 74]. Therefore, if anti-infective drug exposure is associated with the risk of these outcomes, exposure to these drugs should be assessed

during this period. To our knowledge, study 4 is the only available study in the literature that assessed the risk of SGA based on this assumption. In addition, most of the associations found in Study 3 and 4 are explained by biological mechanisms that result from the interaction between anti-infective drugs actions and the physiology of preterm birth and SGA. Biological plausibility is lacking in previous studies that investigated these outcomes [11, 13, 122, 123, 127, 139, 153, 215].

6.1.1.4. Increased statistical power to detect rare outcomes

The ability to test hypotheses in analyses of associations depends on having a sufficient number of outcomes, anticipated magnitude of the association, and prevalence of exposure. As one of the largest pregnancy cohort in the world, the Quebec Pregnancy Registry ensured sufficient power for the targetted effect sizes for the risk of preterm birth and SGA after exposure to anti-infective drugs.

Our studies on the prevalence, predictors and trends of anti-infective drugs use, were based on 97 680 subjects, which gave a very accurate picture of the use of these drugs during pregnancy, and furnished prevalence estimates for comparisons purposes. One of the largest available studies on the subject, analyzed data on 41 293 pregnant women in Germany [2].

Study 3 and 4 analyzed data on 4650 cases of preterm birth and 8192 cases of SGA, respectively. Considering the prevalence of exposure for anti-infective drugs in the general population of 18%, and a type I error of 0.05, these studies had a statistical power of 0.87 to detect a 10% increase in the risk of preterm birth or SGA, which includes all the significant associations found (www.biostat.mc.vanderbilt.edu/wiki/main/PowerSampleSize). If meta-analysis and systematic reviews are excluded (see Table 5 and 6), our

studies have the larger statistical power of all the available etiologic studies in which these outcomes are the principal outcomes of interest.

6.1.1.5. Lack of Recall bias

The use of RAMQ database to assess drug exposure offers the advantage of avoiding recall bias, a major source of potential bias in observational research. This kind of information bias arises as a result of differential recall between cases and controls with regards to medication exposure that occurred at the beginning of pregnancy [275]. In case-control studies conducted during pregnancy, pregnant women identified as cases may be more likely than controls to recall their drug histories when their babies are born. The use of RAMQ databases allows access to the drug history over a long period of time (one year before and during pregnancy, for study 3 and 4) and for a very large number of subjects in a standardized format. Accurate information on name, dosage, and duration of treatment is, therefore available which could be virtually impossible with other methods of data collection.

6.1.1.6. Control for Confounding

Confounding is one of the major threats to internal validity when conducting epidemiologic studies. It refers to a situation in which the effect of a third variable is correlated with the exposure in a manner that will bias assessment of the outcome of interest [275]. In order for a variable to be considered a confounder, it has to be independently associated with the exposure and the outcome of interest, and it cannot be in the causal pathway. The use of data from administrative databases allows us to adjust for several variables related to anti-infective drug use and the risk of preterm birth and SGA. RAMQ and MedEcho databases give information on several potential confounding

variables, such as socio-economic variables (age, place of residence, welfare status), diagnosis, co-morbidities, indication for use, variables related to the access to the health care system, and concomitant exposure to other medications.

6.1.2. Limitations of the studies

The studies presented in this thesis have some limitations inherent to the use of health administrative databases.

6.1.2.1. Assessment of exposure

The RAMQ prescription drug plan provides information on prescriptions filled. Therefore, dispensing of a prescription does not mean that a patient actually took the medication or was completely compliant with treatment. However, the provincial drug plan requires that the beneficiary pay a portion of the costs for medications. This increases the likelihood that prescriptions that are filled are in fact consumed. In addition, in Study 3 and 4, exposure is defined in a dicothomous manner (yes/no), which means that our estimates are based in at least one consumption of the medication, regardeless the duration of prescription. This a very conservative approach to asses risk of adverse outcomes after exposure to medications. Moreover, it has been demonstrated that most filled prescriptions by pregnant women are taken [278].

6.1.2.2. Assessment of outcome

In study 3, we did not have statistical power to analyze preterm birth in the three subgroups (moderate or late preterm birth – 32 to 36 completed weeks of gestation, very preterm – between 28 and 32 weeks of gestation, and extreme preterm – delivery occurring before 28 weeks). Furthermore, in study

4, our definition of SGA has some drawbacks inherent to the use of the population-based Canadian reference for birth weight and gestational age, such as its cross-sectional nature. The curve is based on the birth weights of different infants born at different gestational ages, rather than longitudinal measurements of the same infants over the course of gestation [263].

The linkage between data on the mother and child's birth weight is not possible for 4% of pregnant women included in the Registry. Some reasons for that is the fact that birth weight is recorded whitin ISQ files, and some deliveries occur outside the province of Quebec. The ISQ database therefore does not contains data on these babies, even if the mother and child will be residents of Quebec after delivery.

6.1.2.3. Information bias

In case-control studies, in which information is obtained from past records, information bias can be introduced if the quality and extent of information obtained is different for cases when compared to controls. If a confounding variable is misclassified, the ability to control in the analysis is compromised. In Study 3 and 4, ICD-9 codes for infections were not validated. Therefore, information bias can be present for these variables. If there is nondifferential misclassification of subjects counted for in these variables, the estimates of increased risk of preterm birth and SGA after exposure to anti-infective drugs tends to be diluted, and actually can be an underestimation of the real OR. If nondifferential classification was present for these variables, residual confounding by indication cannot be ruled out.

In what concerns information bias related to the exposure variable, given that the RAMQ prescription drug plan only provides information on prescriptions filled, there is the possibility that some pregnant women did not take their

anti-infective drugs (see section 6.1.2.1). These women could have more severe infections and therefore, an increased risk for preterm birth or SGA. In study 3, if women selected as cases of preterm birth did not actually take their anti-infective drugs, the results of this study could reflect an underestimation of the protective effect of the exposure to anti-infective drugs on the risk of preterm birth. On the other hand, if women selected as controls did not take their anti-infectives, the results of the study 4 could be an overestimation of the effect of SXT on the risk of SGA.

Given that 10% of women with bacterial vaginosis and UTIs are asymptomatic (and that in our analysis, this variable is dichotomously coded), is it possible that some subjects were misclassified for these variables. Women considered having a diagnosis of UTI can represent subjects with more severe cases. In addition, women considered not having sucg diagnosis can actually have less severe asymptomatic forms of infections. However, misclassification for these ariables, if exists, is probably nondiferential. Independent nondifferential misclassification of a dichotomous confounding variable reduce the extent to which the confounder can be controlled, causing a bias in the direction of the confounding variable [279]. This fact may generate distortions produced by uncorrect ascertainement of subjects into different analisys strata, which can partly explain some of the associations found in studies 3 and 4. However, given the low prevalence of asymptomatic cases, and the results of the sensitivity analises (Study 3), we don’t believe that these limitation undermine our conclusions.

6.1.2.4. Confounding by indication and lack of data on life styles factors and socio-demographic characteristics

Confounding by indication occurs when a potential association between exposure to a medication and a given outcome is masked or enhanced by severity of the indication for which the medication was prescribed. To handle the problem of confounding by indication in our studies, we used multivariate logistic regression models to generate adjusted odds ratio, by simultaneously controlling for diagnosis of infections. However, given that we did not have information on severity of infections, it is possible that confounding by indication could partially explain some results of study 3 and 4. In fact, the North American UTI Collaborative Alliance (NAUTICA) showed that the rate of uropathogens resistance against SXT is 21%, whereas the reported resistance rate for nitrofurantoin is only 1.6% [280]. Therefore, women treated with SXT could present more severe forms of UTI, when compared to women exposed to nitrofurantoin. Furtheremore, women treated with SXT could present UTI sub-optimally treated, which can increase the risk of preterm birth and SGA.

Confounding by indication can also explain the increased risk of preterm birth after exposure to metronidazole (Study 3). This drug is used for the treatment of BV, a condition itself associated with preterm birth (see section 2.2.2.). In the multivariate analysis, BV was accounted for in the ICD-9 codes for PID (614-616), which is a broad classification group. Therefore, the associations measured for metronidazole could be a reflection of the effects of BV on the risk of preterm birth.

Most of the RCT that showed no beneficial effects of anti-infectives on pre-term delivery, were trials designed to evaluate the comparative efficacy of these drugs used by pregnant women in hospital settings. In these trials, the

reference group consisted of women with infections (and therefore, at risk of preterm delivery) treated with an anti-infective drug, against which the agent of interest was compared. Some hypothesis can be generated in order to explain why those trials did not show benefit, when compared to the results of study 3: 1) RCT of comparative efficacy sometimes lack statistical power to detect significant differences between two groups with the same condition and exposed to different interventions. These studies did not explore the use of all combined anti-infective drugs; 2) Study 3 is a case-control study where the reference category consists of pregnant women without preterm birth. It is possible that women treated with different anti-infective drugs had different severity of infections, and therefore different baseline risk for preterm birth. As stated before, the results of study 3 can have the influence of confounding by indication.

Administrative databases are a cost-effective source of data for health services research, but lack of data on life styles factors and socio-demographic characteristics are the main criticisms. Indeed, we were unable to measure some risk factors for preterm birth and SGA, such as the gestational intake of illicit substances, alcohol, and caffeine. In study 3, there is a possibility of residual confounding due to the absence of adjustement for previous history of preterm birth, a known risk factors for preterm birth and that can also be associated with infections. Furtheremore, in Study 4, residual confounding due to smoking can partially explain the association found between exposure to SXT and SGA. Smoking is a know risk factor for SGA and is associated with lower socio-economic status as well. Data on maternal height and weight are also lacking in the Quebec Pregnancy Registry. Therefore, residual confounding and confounding by indication may be present.

6.1.2.5. External validity

Women included in the Quebec Pregnancy Registry are those who are covered by the RAMQ prescription drug plan for their medications. Therefore, this cohort may over represent women with lower socioeconomic status, which might affect the generalisability of some findings that may be more strongly associated with socio-demographic factors. However, it has been previously shown that in the Quebec Pregnancy Registry, socioeconomic status is an effect modifier, and thus doesn't affect internal validity of the etiologic studies presented in this thesis (Study 3 and 4) [257]. In addition, pregnant women insured by the RAMQ drug plan and those insured by private drug insurance plans have been shown to have comparable co-morbidity profiles and access to health care services, such as physician visits and hospitalizations.

External validity and selection bias can be tanglible limitations for Study 1 and 2, which are based in prescription practices and the use of anti-infectives among women of lower socio-economical status. Individuals of lower socio-economical status have a higher probability of having infections and therefore, used more anti-infective drugs, implying that the results of Study 1 and 2 are overrepresented. This selection bias can provide inconsistent estimators of prevalence [281]. As stated before, there are substantial differences between pregnant women insured by the Quebec's Public Drug Insurance Plan and those insured by private drug insurance plans (see section 4.1). For this reason, results for predictors and trends of use, and types of anti-infective drugs found in these studies cannot be extrapolated for international comparisons.

6.1.2.6. Multiple testing

Finally, we cannot exclude the possibility of chance findings for 5% of our statistically significant associations due to the number of comparisons made in our studies. Furthermore, multiple testing could partially explain some of our results.

Chapter 7
CLINICAL IMPLICATIONS AND RESEARCH AGENDA

The United Nations Millennium Development Goals 4 and 5 target a two-third reduction in the deaths of children under five years old and a 75% reduction in the maternal mortality ratio between the years 1990 and 2015 [251]. Complications of preterm birth and infants born SGA are the leading direct cause and major risk factor for neonatal deaths and morbidity [160]. Approximately 45–50% of preterm births are idiopathic, and infections are one of the main modifiable causes of preterm birth and SGA. Given the social and economic burden of these adverse pregnancy outcomes, the development of strategies to improve access to effective anti-infective treatment of maternal infections must remain a top research and operational priority. Developing such strategies will depend on the design of evidence-based studies that furnish improved estimates of the impact of such use on the health of the mother and children [174].

This thesis provided knowledge on the use of anti-infective drugs during pregnancy that can be useful for health care professionals and pregnant women. First, it was demonstrated that the use of these drugs during pregnancy is prevalent, and decreases once pregnancy is diagnosed. A decrease in the gestational use of broad-spectrum agents was also observed. Prescribers seem to be concerned with the choice of older and well-known drugs with better safety profiles, such as penicillins. In our study, women that use these medications in the beginning of pregnancy belong to a low socio-economic class and have poorer health. The main indications for the use of these agents during pregnancy are known risk factors for adverse pregnancy outcomes, such as UTIs and pelvic inflammatory disease.

Second, our results indicate that treatment with anti-infective drugs reduces the risk of preterm birth. Pregnant women that used penicillins and macrolides during the last two trimesters of gestation had a 35% decrease in the risk. In addition, results suggest that azithromycin can be an efficient substitute for less efficacious agents in the treatment of infections that predispose to preterm birth. Furthermore, some subgroup of women can have more benefit from treatment, such as women with preterm rupture of membranes. Our results also demonstrated that pregnant women exposed to sulfamethoxazole-trimethoprim had their risk of SGA increased by 60%, whereas the use of nitrofurantoin decreased the risk. Moreover, our results suggest that metronidazole should not be used alone for the prevention of preterm birth. However, the safety profile of its use in association with other agents must be further evaluated.

Pregnant women diagnosed with infections during gestation must be closely monitored in order to avoid adverse impacts on pregnancy outcomes. The results of this thesis suggest that health care professionals must consider other therapeutic alternatives to metronidazole and sulfonamides, and special attention must be given to the evaluation of the benefit of treating subgroups of women with other risk factors for preterm birth or SGA.

This study generated some research questions that would need to be addressed in future studies. Given its potential in preventing preterm birth, the safety profile of azithromycin during pregnancy must be further evaluated. In addition, more studies evaluating the effectiveness and safety of the use of metronidazole in association with other agents are needed. Other therapeutic alternatives to sulfonamides in the treatment of UTIs must be investigated and their safety profiles must be established. Finally, specific clinical guidelines with recommendations for the use of anti-infective drugs during gestation must be developed.

Chapter 8

REFERENCES

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1. Philipson, A., *The use of antibiotics in pregnancy.* J Antimicrob Chemother, 1983. **12**(2): p. 101-2.
2. Amann, U., et al., *Antibiotics in pregnancy: analysis of potential risks and determinants in a large German statutory sickness fund population.* Pharmacoepidemiol Drug Saf, 2006. **15**(5): p. 327-37.
3. Czeizel, A.E., M. Rockenbauer, and J. Olsen, *Use of antibiotics during pregnancy.* Eur J Obstet Gynecol Reprod Biol, 1998. **81**(1): p. 1-8.
4. Splinter, M.Y., et al., *Prenatal use of medications by women giving birth at a university hospital.* South Med J, 1997. **90**(5): p. 498-502.
5. Jamieson, D.J., R.N. Theiler, and S.A. Rasmussen, *Emerging infections and pregnancy.* Emerg Infect Dis, 2006. **12**(11): p. 1638-43.
6. Rasmussen, S.A., et al., *Emerging infections and pregnancy: assessing the impact on the embryo or fetus.* Am J Med Genet A, 2007. **143A**(24): p. 2896-903.
7. Oyarzun, E., et al., *Antibiotic treatment in preterm labor and intact membranes: a randomized, double-blinded, placebo-controlled trial.* J Matern Fetal Med, 1998. **7**(3): p. 105-10.
8. Lee, M., et al., *Urinary tract infections in pregnancy.* Can Fam Physician, 2008. **54**(6): p. 853-4.
9. Lundgren, E.M. and T. Tuvemo, *Effects of being born small for gestational age on long-term intellectual performance.* Best Pract Res Clin Endocrinol Metab, 2008. **22**(3): p. 477-88.
10. Sheffield, J.S. and F.G. Cunningham, *Urinary tract infection in women.* Obstet Gynecol, 2005. **106**(5 Pt 1): p. 1085-92.

11. Mittal, P. and D.A. Wing, *Urinary tract infections in pregnancy.* Clin Perinatol, 2005. **32**(3): p. 749-64.
12. Lockitch, G., *Maternal-fetal risk assessment.* Clin Biochem, 2004. **37**(6): p. 447-9.
13. Wen, S.W., et al., *Maternal exposure to folic acid antagonists and placenta-mediated adverse pregnancy outcomes.* CMAJ, 2008. **179**(12): p. 1263-8.
14. Dashe, J.S. and L.C. Gilstrap, 3rd, *Antibiotic use in pregnancy.* Obstet Gynecol Clin North Am, 1997. **24**(3): p. 617-29.
15. Sapadin, A.N. and R. Fleischmajer, *Tetracyclines: nonantibiotic properties and their clinical implications.* J Am Acad Dermatol, 2006. **54**(2): p. 258-65.
16. Altenburg, J., et al., *Immunomodulatory effects of macrolide antibiotics - part 1: biological mechanisms.* Respiration, 2011. **81**(1): p. 67-74.
17. Locksmith, G. and P. Duff, *Infection, antibiotics, and preterm delivery.* Semin Perinatol, 2001. **25**(5): p. 295-309.
18. McGregor, J.A. and J.I. French, *Preterm Birth: The Role of Infection and Inflammation.* Medscape Womens Health, 1997. **2**(8): p. 1.
19. Romero, R., et al., *The role of inflammation and infection in preterm birth.* Semin Reprod Med, 2007. **25**(1): p. 21-39.
20. Nahum, G.G., K. Uhl, and D.L. Kennedy, *Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks.* Obstet Gynecol, 2006. **107**(5): p. 1120-38.
21. Vangapandu, S.N., et al., *Recent patents on proteases and kinases as anti-infective agents: a review.* Recent Pat Antiinfect Drug Discov, 2006. **1**(2): p. 209-24.
22. Waksman, S.A., *Successes and failures in the search for antibiotics.* Adv Appl Microbiol, 1969. **11**: p. 1-16.

23. von Nussbaum, F., et al., *Antibacterial natural products in medicinal chemistry--exodus or revival?* Angew Chem Int Ed Engl, 2006. **45**(31): p. 5072-129.
24. Joseph DiPiro, R.T., Gary Yee, Gary Matzke, Barbara Wells, L. Michael Posey, *Pharmacotherapy: A Pathophysiologic Approach*. 8th ed. 2011: McGraw-Hill Medical.
25. Cuddy, P.G., *Antibiotic classification: implications for drug selection.* Crit Care Nurs Q, 1997. **20**(3): p. 89-102.
26. Hogberg, L.D., A. Heddini, and O. Cars, *The global need for effective antibiotics: challenges and recent advances.* Trends Pharmacol Sci, 2010. **31**(11): p. 509-15.
27. Bush, K. and M.J. Macielag, *New beta-lactam antibiotics and beta-lactamase inhibitors.* Expert Opin Ther Pat, 2010. **20**(10): p. 1277-93.
28. Kirst, H.A., *New macrolide, lincosaminide and streptogramin B antibiotics.* Expert Opin Ther Pat, 2010. **20**(10): p. 1343-57.
29. Ding, C. and J. He, *Effect of antibiotics in the environment on microbial populations.* Appl Microbiol Biotechnol, 2010. **87**(3): p. 925-41.
30. Niebyl, J.R., *Antibiotics and other anti-infective agents in pregnancy and lactation.* Am J Perinatol, 2003. **20**(8): p. 405-14.
31. Norwitz, E.R. and J.A. Greenberg, *Antibiotics in pregnancy: are they safe?* Rev Obstet Gynecol, 2009. **2**(3): p. 135-6.
32. Workowski, K.A. and S. Berman, *Sexually transmitted diseases treatment guidelines, 2010.* MMWR Recomm Rep, 2010. **59**(RR-12): p. 1-110.
33. Einarson, A., S. Shuhaiber, and G. Koren, *Effects of antibacterials on the unborn child: what is known and how should this influence prescribing.* Paediatr Drugs, 2001. **3**(11): p. 803-16.
34. Rubin, R.H., et al., *Evaluation of new anti-infective drugs for the treatment of urinary tract infection. Infectious Diseases Society of*

America and the Food and Drug Administration. Clin Infect Dis, 1992. **15 Suppl 1**: p. S216-27.

35. Sivojelezova, A., et al., *Trimethoprim-sulfonamide combination therapy in early pregnancy.* Can Fam Physician, 2003. **49**: p. 1085-6.
36. Berkovitch, M., et al., *Safety of the new quinolones in pregnancy.* Obstet Gynecol, 1994. **84**(4): p. 535-8.
37. Le, J., et al., *Urinary tract infections during pregnancy.* Ann Pharmacother, 2004. **38**(10): p. 1692-701.
38. Lain, S.J., et al., *A survey of acute self-reported infections in pregnancy.* BMJ Open, 2011. **1**(1): p. e000083.
39. Larsson, P.G., et al., *Bacterial vaginosis. Transmission, role in genital tract infection and pregnancy outcome: an enigma.* APMIS, 2005. **113**(4): p. 233-45.
40. Desai, M. and S. Dellicour, *Effects of malaria and its treatment in early pregnancy.* Lancet Infect Dis, 2011.
41. Dotters-Katz, S., J. Kuller, and R.P. Heine, *Parasitic infections in pregnancy.* Obstet Gynecol Surv, 2011. **66**(8): p. 515-25.
42. Williams, J., *Blood tests for investigating maternal wellbeing. 5. Testing for sexually transmitted infections in pregnancy.* Pract Midwife, 2011. **14**(2): p. 36-41.
43. Haas, A. and G. Maschmeyer, *[Antibiotic therapy in pregnancy].* Dtsch Med Wochenschr, 2008. **133**(11): p. 511-5.
44. Sa del Fiol, F., M. Gerenutti, and F.C. Groppo, *Antibiotics and pregnancy.* Pharmazie, 2005. **60**(7): p. 483-93.
45. Gums, J.G., *Redefining appropriate use of antibiotics.* Am Fam Physician, 2004. **69**(1): p. 35, 39-40.
46. Aviv, R.I., K. Chubb, and S.W. Lindow, *The prevalence of maternal medication ingestion in the antenatal period.* S Afr Med J, 1993. **83**(9): p. 657-60.

47. Fonseca, M.R., E. Fonseca, and G. Bergsten-Mendes, *[Prevalence of drug use during pregnancy: a pharmacoepidemiological approach].* Rev Saude Publica, 2002. **36**(2): p. 205-12.
48. Lugo NT, F.R., Cárdenas MSL, Ermeso GA, *Uso de medicamentos durante el embarazo y su posible efecto teratogénico.* Rev Cubana Med. Gen. Integr, 2004. **20**(4): p. 8.
49. Olesen, C., et al., *Drug use in first pregnancy and lactation: a population-based survey among Danish women. The EUROMAP group.* Eur J Clin Pharmacol, 1999. **55**(2): p. 139-44.
50. Heikkila, A.M., *Antibiotics in pregnancy--a prospective cohort study on the policy of antibiotic prescription.* Ann Med, 1993. **25**(5): p. 467-71.
51. Henry, A. and C. Crowther, *Patterns of medication use during and prior to pregnancy: the MAP study.* Aust N Z J Obstet Gynaecol, 2000. **40**(2): p. 165-72.
52. Chamany, S., et al., *Knowledge, attitudes, and reported practices among obstetrician-gynecologists in the USA regarding antibiotic prescribing for upper respiratory tract infections.* Infect Dis Obstet Gynecol, 2005. **13**(1): p. 17-24.
53. Piper, J.M., et al., *Maternal use of prescribed drugs associated with recognized fetal adverse drug reactions.* Am J Obstet Gynecol, 1988. **159**(5): p. 1173-7.
54. Petersen, I., et al., *Oral antibiotic prescribing during pregnancy in primary care: UK population-based study.* J Antimicrob Chemother, 2010. **65**(10): p. 2238-46.
55. Gendron, M.P., et al., *Health care providers' requests to Teratogen Information Services on medication use during pregnancy and lactation.* Eur J Clin Pharmacol, 2009. **65**(5): p. 523-31.
56. Wise, R., *Prescribing in pregnancy: antibiotics.* BRITISH MEDICAL JOURNAL, 1987. **294**: p. 4.

57. *Prevention of group B streptococcal infection in newborns: recommendation statement from the Canadian Task Force on Preventive Health Care.* CMAJ, 2002. **166**(7): p. 928-30.
58. Ledger, W.J., *Prophylactic antibiotics in obstetrics-gynecology: a current asset, a future liability?* Expert Rev Anti Infect Ther, 2006. **4**(6): p. 957-64.
59. Laibl, V. and J. Sheffield, *The management of respiratory infections during pregnancy.* Immunol Allergy Clin North Am, 2006. **26**(1): p. 155-72, viii.
60. *Information from your family docter. Respiratory infections during pregnancy.* Am Fam Physician, 2005. **72**(8): p. 1583-4.
61. Lim, W.S., J.T. Macfarlane, and C.L. Colthorpe, *Treatment of community-acquired lower respiratory tract infections during pregnancy.* Am J Respir Med, 2003. **2**(3): p. 221-33.
62. Pirotta, M., K.A. Fethers, and C.S. Bradshaw, *Bacterial vaginosis - More questions than answers.* Aust Fam Physician, 2009. **38**(6): p. 394-7.
63. Duarte, G., et al., *[Urinary tract infection in pregnancy].* Rev Bras Ginecol Obstet, 2008. **30**(2): p. 93-100.
64. Wagenlehner, F.M., W. Weidner, and K.G. Naber, *An update on uncomplicated urinary tract infections in women.* Curr Opin Urol, 2009. **19**(4): p. 368-74.
65. Jolley, J.A. and D.A. Wing, *Pyelonephritis in pregnancy: an update on treatment options for optimal outcomes.* Drugs, 2010. **70**(13): p. 1643-55.
66. Macejko, A.M. and A.J. Schaeffer, *Asymptomatic bacteriuria and symptomatic urinary tract infections during pregnancy.* Urol Clin North Am, 2007. **34**(1): p. 35-42.

67. Gilstrap, L.C., 3rd, F.G. Cunningham, and P.J. Whalley, *Acute pyelonephritis in pregnancy: an anterospective study.* Obstet Gynecol, 1981. **57**(4): p. 409-13.
68. Hill, J.B., et al., *Acute pyelonephritis in pregnancy.* Obstet Gynecol, 2005. **105**(1): p. 18-23.
69. Sharma, P. and L. Thapa, *Acute pyelonephritis in pregnancy: a retrospective study.* Aust N Z J Obstet Gynaecol, 2007. **47**(4): p. 313-5.
70. Ovalle, A., et al., *[Pre-existing diseases as risk factors and prognosis of genito-urinary infection in pregnancy].* Rev Chil Obstet Ginecol, 1989. **54**(6): p. 341-7.
71. Harris, R.E. and L.C. Gilstrap, 3rd, *Cystitis during pregnancy: a distinct clinical entity.* Obstet Gynecol, 1981. **57**(5): p. 578-80.
72. Millar, L.K. and S.M. Cox, *Urinary tract infections complicating pregnancy.* Infect Dis Clin North Am, 1997. **11**(1): p. 13-26.
73. MacLean, A.B., *Urinary tract infection in pregnancy.* Int J Antimicrob Agents, 2001. **17**(4): p. 273-6; discussion 276-7.
74. Shand, D.G., et al., *Relation between residual urine volume and response to treatment of urinary infection.* Lancet, 1970. **760**(1): p. 1305-6.
75. Gratacos, E., et al., *Screening and treatment of asymptomatic bacteriuria in pregnancy prevent pyelonephritis.* J Infect Dis, 1994. **169**(6): p. 1390-2.
76. Schieve, L.A., et al., *Urinary tract infection during pregnancy: its association with maternal morbidity and perinatal outcome.* Am J Public Health, 1994. **84**(3): p. 405-10.
77. Rosen, D.A., et al., *Detection of intracellular bacterial communities in human urinary tract infection.* PLoS Med, 2007. **4**(12): p. e329.
78. Neal, D.E., Jr., *Complicated urinary tract infections.* Urol Clin North Am, 2008. **35**(1): p. 13-22; v.

79. Conde-Agudelo, A., J. Villar, and M. Lindheimer, *Maternal infection and risk of preeclampsia: systematic review and metaanalysis.* Am J Obstet Gynecol, 2008. **198**(1): p. 7-22.
80. Rustveld, L.O., S.F. Kelsey, and R. Sharma, *Association between maternal infections and preeclampsia: a systematic review of epidemiologic studies.* Matern Child Health J, 2008. **12**(2): p. 223-42.
81. Fede, T., *Urinary tract infection and anemia in pregnancy.* Clin Exp Obstet Gynecol, 1983. **10**(2-3): p. 140-1.
82. Delzell, J.E., Jr. and M.L. Lefevre, *Urinary tract infections during pregnancy.* Am Fam Physician, 2000. **61**(3): p. 713-21.
83. Simmons, L.E., et al., *Preventing preterm birth and neonatal mortality: exploring the epidemiology, causes, and interventions.* Semin Perinatol, 2010. **34**(6): p. 408-15.
84. McDermott, S., et al., *Urinary tract infections during pregnancy and mental retardation and developmental delay.* Obstet Gynecol, 2000. **96**(1): p. 113-9.
85. Broman, S.H., *Prenatal risk factors for mental retardation in young children.* Public Health Rep, 1987. **102**(4 Suppl): p. 55-57.
86. Gilstrap, L.C., 3rd and S.M. Ramin, *Urinary tract infections during pregnancy.* Obstet Gynecol Clin North Am, 2001. **28**(3): p. 581-91.
87. Bruel, H., et al., *[Hemolytic anemia in a newborn after maternal treatment with nitrofurantoin at the end of pregnancy].* Arch Pediatr, 2000. **7**(7): p. 745-7.
88. Cimolai, N. and T. Cimolai, *Nitrofurantoin and pregnancy.* CMAJ, 2007. **176**(13): p. 1860-1.
89. Guinto, V.T., et al., *Different antibiotic regimens for treating asymptomatic bacteriuria in pregnancy.* Cochrane Database Syst Rev, 2010(9): p. CD007855.

90. Milo, G., et al., *Duration of antibacterial treatment for uncomplicated urinary tract infection in women.* Cochrane Database Syst Rev, 2005(2): p. CD004682.

91. Christensen, B., *Which antibiotics are appropriate for treating bacteriuria in pregnancy?* J Antimicrob Chemother, 2000. **46 Suppl 1**: p. 29-34; discussion 63-5.

92. Connolly, A. and J.M. Thorp, Jr., *Urinary tract infections in pregnancy.* Urol Clin North Am, 1999. **26**(4): p. 779-87.

93. Ovalle, A. and M. Levancini, *Urinary tract infections in pregnancy.* Curr Opin Urol, 2001. **11**(1): p. 55-9.

94. Vazquez, J.C. and J. Villar, *Treatments for symptomatic urinary tract infections during pregnancy.* Cochrane Database Syst Rev, 2003(4): p. CD002256.

95. Wing, D.A., *Pyelonephritis.* Clin Obstet Gynecol, 1998. **41**(3): p. 515-26.

96. Nelson, D.B. and G. Macones, *Bacterial vaginosis in pregnancy: current findings and future directions.* Epidemiol Rev, 2002. **24**(2): p. 102-8.

97. Minkoff, H., et al., *Risk factors for prematurity and premature rupture of membranes: a prospective study of the vaginal flora in pregnancy.* Am J Obstet Gynecol, 1984. **150**(8): p. 965-72.

98. Modak, T., et al., *Diagnosis of bacterial vaginosis in cases of abnormal vaginal discharge: comparison of clinical and microbiological criteria.* J Infect Dev Ctries, 2011. **5**(5): p. 353-60.

99. Hillier, S.L., et al., *Microbiological, epidemiological and clinical correlates of vaginal colonisation by Mobiluncus species.* Genitourin Med, 1991. **67**(1): p. 26-31.

100. Bruce, F.C., K. Fiscella, and J.S. Kendrick, *Vaginal douching and preterm birth: an intriguing hypothesis.* Med Hypotheses, 2000. **54**(3): p. 448-52.

101. Donders, G.G., *Wet smear compared with Gram stain diagnosis in asymptomatic pregnant women.* Obstet Gynecol, 2001. **97**(3): p. 482.
102. Eschenbach, D.A., et al., *Diagnosis and clinical manifestations of bacterial vaginosis.* Am J Obstet Gynecol, 1988. **158**(4): p. 819-28.
103. Kimberlin, D.F. and W.W. Andrews, *Bacterial vaginosis: association with adverse pregnancy outcome.* Semin Perinatol, 1998. **22**(4): p. 242-50.
104. Morris, M., et al., *Bacterial vaginosis: a public health review.* BJOG, 2001. **108**(5): p. 439-50.
105. Martius, J. and D.A. Eschenbach, *The role of bacterial vaginosis as a cause of amniotic fluid infection, chorioamnionitis and prematurity--a review.* Arch Gynecol Obstet, 1990. **247**(1): p. 1-13.
106. Riggs, M.A. and M.A. Klebanoff, *Treatment of vaginal infections to prevent preterm birth: a meta-analysis.* Clin Obstet Gynecol, 2004. **47**(4): p. 796-807; discussion 881-2.
107. McDonald, H.M., P. Brocklehurst, and A. Gordon, *Antibiotics for treating bacterial vaginosis in pregnancy.* Cochrane Database Syst Rev, 2007(1): p. CD000262.
108. *Screening for bacterial vaginosis in pregnancy to prevent preterm delivery: U.S. Preventive Services Task Force recommendation statement.* Ann Intern Med, 2008. **148**(3): p. 214-9.
109. Joesoef, M.R., et al., *Intravaginal clindamycin treatment for bacterial vaginosis: effects on preterm delivery and low birth weight.* Am J Obstet Gynecol, 1995. **173**(5): p. 1527-31.
110. Lamont, R.F., et al., *Intravaginal clindamycin to reduce preterm birth in women with abnormal genital tract flora.* Obstet Gynecol, 2003. **101**(3): p. 516-22.
111. Vermeulen, G.M. and H.W. Bruinse, *Prophylactic administration of clindamycin 2% vaginal cream to reduce the incidence of spontaneous preterm birth in women with an increased recurrence risk: a*

randomised placebo-controlled double-blind trial. Br J Obstet Gynaecol, 1999. **106**(7): p. 652-7.

112. Tiboni, G.M., F. Marotta, and A.P. Castigliego, *Teratogenic effects in mouse fetuses subjected to the concurrent in utero exposure to miconazole and metronidazole.* Reprod Toxicol, 2008. **26**(3-4): p. 254-61.
113. Einarson, A., E. Ho, and G. Koren, *Can we use metronidazole during pregnancy and breastfeeding? Putting an end to the controversy.* Can Fam Physician, 2000. **46**: p. 1053-4.
114. Andrews, W.W., et al., *Interconceptional antibiotics to prevent spontaneous preterm birth: a randomized clinical trial.* Am J Obstet Gynecol, 2006. **194**(3): p. 617-23.
115. Tita, A.T., et al., *Clinical trial of interconceptional antibiotics to prevent preterm birth: subgroup analyses and possible adverse antibiotic-microbial interaction.* Am J Obstet Gynecol, 2007. **197**(4): p. 367 e1-6.
116. Koren, G., A. Pastuszak, and S. Ito, *Drugs in pregnancy.* N Engl J Med, 1998. **338**(16): p. 1128-37.
117. Goodwin, J., et al., *Counseling regarding pregnancy--related drug exposures by family physicians in Ontario.* Can J Clin Pharmacol, 2007. **14**(1): p. e58-69.
118. Lancaster, P.A., *Causes of birth defects: lessons from history.* Congenit Anom (Kyoto), 2011. **51**(1): p. 2-5.
119. Rasmussen, S.A., et al., *Teratology: from science to birth defects prevention.* Birth Defects Res A Clin Mol Teratol, 2009. **85**(1): p. 82-92.
120. Jepsen, P., et al., *A population-based study of maternal use of amoxicillin and pregnancy outcome in Denmark.* Br J Clin Pharmacol, 2003. **55**(2): p. 216-21.
121. Czeizel, A.E., et al., *Use of cephalosporins during pregnancy and in the presence of congenital abnormalities: a population-based, case-control study.* Am J Obstet Gynecol, 2001. **184**(6): p. 1289-96.

122. Berkovitch, M., et al., *First trimester exposure to cefuroxime: a prospective cohort study.* Br J Clin Pharmacol, 2000. **50**(2): p. 161-5.
123. Berkovitch, M., et al., *First-trimester exposure to amoxycillin/clavulanic acid: a prospective, controlled study.* Br J Clin Pharmacol, 2004. **58**(3): p. 298-302.
124. Einarson, A., et al., *A prospective controlled multicentre study of clarithromycin in pregnancy.* Am J Perinatol, 1998. **15**(9): p. 523-5.
125. Czeizel, A.E., et al., *A case-control teratological study of spiramycin, roxithromycin, oleandomycin and josamycin.* Acta Obstet Gynecol Scand, 2000. **79**(3): p. 234-7.
126. Czeizel, A.E., et al., *A population-based case-control teratologic study of oral erythromycin treatment during pregnancy.* Reprod Toxicol, 1999. **13**(6): p. 531-6.
127. Sarkar, M., et al., *Pregnancy outcome following gestational exposure to azithromycin.* BMC Pregnancy Childbirth, 2006. **6**: p. 18.
128. Bar-Oz, B., et al., *Pregnancy outcome after gestational exposure to the new macrolides: a prospective multi-center observational study.* Eur J Obstet Gynecol Reprod Biol, 2008. **141**(1): p. 31-4.
129. Chun, J.Y., et al., *Fetal outcome following roxithromycin exposure in early pregnancy.* J Matern Fetal Neonatal Med, 2006. **19**(3): p. 189-92.
130. Nesbitt, R.E., Jr. and J.E. Young, *Urinary tract infections during pregnancy and the puerperium; treatment with nitrofurantoin (furadantin).* Obstet Gynecol, 1957. **10**(1): p. 89-94.
131. Hailey, F.J., et al., *Foetal safety of nitrofurantoin macrocrystals therapy during pregnancy: a retrospective analysis.* J Int Med Res, 1983. **11**(6): p. 364-9.
132. Ben David, S., et al., *The safety of nitrofurantoin during the first trimester of pregnancy: meta-analysis.* Fundam Clin Pharmacol, 1995. **9**(5): p. 503-7.

133. Czeizel, A.E., et al., *Nitrofurantoin and congenital abnormalities.* Eur J Obstet Gynecol Reprod Biol, 2001. **95**(1): p. 119-26.
134. Gait, J.E., *Hemolytic reactions to nitrofurantoin in patients with glucose-6-phosphate dehydrogenase deficiency: theory and practice.* DICP, 1990. **24**(12): p. 1210-3.
135. Ratanajamit, C., et al., *Adverse pregnancy outcome in users of sulfamethizole during pregnancy: a population-based observational study.* J Antimicrob Chemother, 2003. **52**(5): p. 837-41.
136. Schaefer, C., et al., *Pregnancy outcome after prenatal quinolone exposure. Evaluation of a case registry of the European Network of Teratology Information Services (ENTIS).* Eur J Obstet Gynecol Reprod Biol, 1996. **69**(2): p. 83-9.
137. Wilton, L.V., G.L. Pearce, and R.D. Mann, *A comparison of ciprofloxacin, norfloxacin, ofloxacin, azithromycin and cefixime examined by observational cohort studies.* Br J Clin Pharmacol, 1996. **41**(4): p. 277-84.
138. Loebstein, R., et al., *Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study.* Antimicrob Agents Chemother, 1998. **42**(6): p. 1336-9.
139. Larsen, H., et al., *Birth outcome following maternal use of fluoroquinolones.* Int J Antimicrob Agents, 2001. **18**(3): p. 259-62.
140. Czeizel, A.E., et al., *A population-based case-control teratologic study of nalidixic acid.* Int J Gynaecol Obstet, 2001. **73**(3): p. 221-8.
141. Warchol, M.E., *Cellular mechanisms of aminoglycoside ototoxicity.* Curr Opin Otolaryngol Head Neck Surg, 2010. **18**(5): p. 454-8.
142. Leroux, L., *[Is there an acquired congenital deafness due to streptomycin?].* Ann Otolaryngol, 1950. **67**(2-3): p. 194-6.
143. Robinson, G.C. and K.G. Cambon, *Hearing Loss in Infants of Tuberculous Mothers Treated with Streptomycin during Pregnancy.* N Engl J Med, 1964. **271**: p. 949-51.

144. Marynowski, A. and E. Sianozecka, *[Comparison of the incidence of congenital malformations in neonates from healthy mothers and from patients treated for tuberculosis].* Ginekol Pol, 1972. **43**(6): p. 713-5.
145. de Hoog, M., et al., *Newborn hearing screening: tobramycin and vancomycin are not risk factors for hearing loss.* J Pediatr, 2003. **142**(1): p. 41-6.
146. Antonini, L.G. and H.U. Luder, *Discoloration of teeth from tetracyclines--even today?* Schweiz Monatsschr Zahnmed, 2011. **121**(5): p. 414-31.
147. Forti, G. and C. Benincori, *Doxycycline and the teeth.* Lancet, 1969. **1**(7598): p. 782.
148. Briggs GG, F.R., Yaffe SJ, *Drugs in pregnancy and lactation*. 8th ed. 2008, Bartimore: Lippincott Williams & Wilkins.
149. Czeizel, A.E. and M. Rockenbauer, *Teratogenic study of doxycycline.* Obstet Gynecol, 1997. **89**(4): p. 524-8.
150. Czeizel, A.E. and M. Rockenbauer, *A population-based case-control teratologic study of oral oxytetracycline treatment during pregnancy.* Eur J Obstet Gynecol Reprod Biol, 2000. **88**(1): p. 27-33.
151. Czeizel, A.E. and M. Rockenbauer, *A population based case-control teratologic study of oral metronidazole treatment during pregnancy.* Br J Obstet Gynaecol, 1998. **105**(3): p. 322-7.
152. Czeizel, A.E., et al., *A population-based case-control teratologic study of oral chloramphenicol treatment during pregnancy.* Eur J Epidemiol, 2000. **16**(4): p. 323-7.
153. Diav-Citrin, O., et al., *Pregnancy outcome after gestational exposure to metronidazole: a prospective controlled cohort study.* Teratology, 2001. **63**(5): p. 186-92.
154. Piper, J.M., E.F. Mitchel, and W.A. Ray, *Prenatal use of metronidazole and birth defects: no association.* Obstet Gynecol, 1993. **82**(3): p. 348-52.

155. Cooper, W.O., et al., *Antibiotics potentially used in response to bioterrorism and the risk of major congenital malformations.* Paediatr Perinat Epidemiol, 2009. **23**(1): p. 18-28.
156. Crider, K.S., et al., *Antibacterial medication use during pregnancy and risk of birth defects: National Birth Defects Prevention Study.* Arch Pediatr Adolesc Med, 2009. **163**(11): p. 978-85.
157. Mastroiacovo, P., et al., *Prospective assessment of pregnancy outcomes after first-trimester exposure to fluconazole.* Am J Obstet Gynecol, 1996. **175**(6): p. 1645-50.
158. Goldenberg, R.L., et al., *Epidemiology and causes of preterm birth.* Lancet, 2008. **371**(9606): p. 75-84.
159. Bittar, R.E. and M. Zugaib, *[Risk predictors for preterm birth].* Rev Bras Ginecol Obstet, 2009. **31**(4): p. 203-9.
160. Beck, S., et al., *The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity.* Bull World Health Organ, 2010. **88**(1): p. 31-8.
161. Ofori, B.D., M. Le Tiec, and A. Berard, *Risk factors associated with preterm birth according to gestational age at birth.* Pharmacoepidemiol Drug Saf, 2008. **17**(6): p. 556-64.
162. Canada, P.H.A.o., *Canadian Perinatal Health Report 2008*. 2008: Ottawa.
163. Ananth, C.V. and A.M. Vintzileos, *Epidemiology of preterm birth and its clinical subtypes.* J Matern Fetal Neonatal Med, 2006. **19**(12): p. 773-82.
164. Mercer, B.M., et al., *The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network.* Am J Obstet Gynecol, 1999. **181**(5 Pt 1): p. 1216-21.

165. Fuentes-Afflick, E. and N.A. Hessol, *Interpregnancy interval and the risk of premature infants.* Obstet Gynecol, 2000. **95**(3): p. 383-90.
166. Morgan-Ortiz, F., et al., *[Sociodemographic and obstetric factors associated with preterm birth].* Ginecol Obstet Mex, 2010. **78**(2): p. 103-9.
167. Morgan-Ortiz, F., et al., *[Effect of post-abortion interpregnancy interval on obstetric and perinatal outcomes].* Ginecol Obstet Mex, 2010. **78**(1): p. 46-52.
168. Ancel, P.Y., et al., *History of induced abortion as a risk factor for preterm birth in European countries: results of the EUROPOP survey.* Hum Reprod, 2004. **19**(3): p. 734-40.
169. Andrews, W.W., R.L. Goldenberg, and J.C. Hauth, *Preterm labor: emerging role of genital tract infections.* Infect Agents Dis, 1995. **4**(4): p. 196-211.
170. Kemp, M.W., et al., *Preterm birth, infection, and inflammation advances from the study of animal models.* Reprod Sci, 2010. **17**(7): p. 619-28.
171. Randis, T.M., *Progress toward improved understanding of infection-related preterm birth.* Clin Perinatol, 2010. **37**(3): p. 677-88.
172. Petrou, S., *The economic consequences of preterm birth during the first 10 years of life.* BJOG, 2005. **112 Suppl 1**: p. 10-5.
173. Petrou, S., et al., *The impact of preterm birth on hospital inpatient admissions and costs during the first 5 years of life.* Pediatrics, 2003. **112**(6 Pt 1): p. 1290-7.
174. Iams, J.D., et al., *Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth.* Lancet, 2008. **371**(9607): p. 164-75.
175. Barros, F.C., et al., *Global report on preterm birth and stillbirth (3 of 7): evidence for effectiveness of interventions.* BMC Pregnancy Childbirth, 2010. **10 Suppl 1**: p. S3.

176. Lumley, J., et al., *Interventions for promoting smoking cessation during pregnancy.* Cochrane Database Syst Rev, 2009(3): p. CD001055.
177. Mercer, B., C. Milluzzi, and M. Collin, *Periviable birth at 20 to 26 weeks of gestation: proximate causes, previous obstetric history and recurrence risk.* Am J Obstet Gynecol, 2005. **193**(3 Pt 2): p. 1175-80.
178. Smith, V., et al., *A systematic review and quality assessment of systematic reviews of randomised trials of interventions for preventing and treating preterm birth.* Eur J Obstet Gynecol Reprod Biol, 2009. **142**(1): p. 3-11.
179. Goldenberg, R.L., J.C. Hauth, and W.W. Andrews, *Intrauterine infection and preterm delivery.* N Engl J Med, 2000. **342**(20): p. 1500-7.
180. Romero, R., et al., *Infection and labor. III. Interleukin-1: a signal for the onset of parturition.* Am J Obstet Gynecol, 1989. **160**(5 Pt 1): p. 1117-23.
181. Romero, R., et al., *Neutrophil attractant/activating peptide-1/interleukin-8 in term and preterm parturition.* Am J Obstet Gynecol, 1991. **165**(4 Pt 1): p. 813-20.
182. Adams Waldorf, K.M., C.E. Rubens, and M.G. Gravett, *Use of nonhuman primate models to investigate mechanisms of infection-associated preterm birth.* BJOG, 2011. **118**(2): p. 136-44.
183. Newton, E.R., M.J. Dinsmoor, and R.S. Gibbs, *A randomized, blinded, placebo-controlled trial of antibiotics in idiopathic preterm labor.* Obstet Gynecol, 1989. **74**(4): p. 562-6.
184. Eschenbach, D.A., et al., *A randomized placebo-controlled trial of erythromycin for the treatment of Ureaplasma urealyticum to prevent premature delivery. The Vaginal Infections and Prematurity Study Group.* Am J Obstet Gynecol, 1991. **164**(3): p. 734-42.

185. Newton, E.R., et al., *Combination antibiotics and indomethacin in idiopathic preterm labor: a randomized double-blind clinical trial.* Am J Obstet Gynecol, 1991. **165**(6 Pt 1): p. 1753-9.

186. Romero, R., et al., *Antibiotic treatment of preterm labor with intact membranes: a multicenter, randomized, double-blinded, placebo-controlled trial.* Am J Obstet Gynecol, 1993. **169**(4): p. 764-74.

187. Watts, D.H., et al., *Randomized trial of antibiotics in addition to tocolytic therapy to treat preterm labor.* Infect Dis Obstet Gynecol, 1994. **1**(5): p. 220-7.

188. Gordon, M., et al., *A randomized, prospective study of adjunctive ceftizoxime in preterm labor.* Am J Obstet Gynecol, 1995. **172**(5): p. 1546-52.

189. Cox, S.M., et al., *Randomized investigation of antimicrobials for the prevention of preterm birth.* Am J Obstet Gynecol, 1996. **174**(1 Pt 1): p. 206-10.

190. Kenyon, S.L., D.J. Taylor, and W. Tarnow-Mordi, *Broad-spectrum antibiotics for spontaneous preterm labour: the ORACLE II randomised trial. ORACLE Collaborative Group.* Lancet, 2001. **357**(9261): p. 989-94.

191. Kenyon, S.L., D.J. Taylor, and W. Tarnow-Mordi, *Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomised trial. ORACLE Collaborative Group.* Lancet, 2001. **357**(9261): p. 979-88.

192. Norman, K., et al., *Ampicillin and metronidazole treatment in preterm labour: a multicentre, randomised controlled trial.* Br J Obstet Gynaecol, 1994. **101**(5): p. 404-8.

193. Morales, W.J., S. Schorr, and J. Albritton, *Effect of metronidazole in patients with preterm birth in preceding pregnancy and bacterial vaginosis: a placebo-controlled, double-blind study.* Am J Obstet Gynecol, 1994. **171**(2): p. 345-7; discussion 348-9.

194. Hauth, J.C., et al., *Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis.* N Engl J Med, 1995. **333**(26): p. 1732-6.

195. Svare, J., et al., *Ampicillin-metronidazole treatment in idiopathic preterm labour: a randomised controlled multicentre trial.* Br J Obstet Gynaecol, 1997. **104**(8): p. 892-7.

196. McDonald, H.M., et al., *Impact of metronidazole therapy on preterm birth in women with bacterial vaginosis flora (Gardnerella vaginalis): a randomised, placebo controlled trial.* Br J Obstet Gynaecol, 1997. **104**(12): p. 1391-7.

197. Carey, J.C., et al., *Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units.* N Engl J Med, 2000. **342**(8): p. 534-40.

198. Klebanoff, M.A., et al., *Failure of metronidazole to prevent preterm delivery among pregnant women with asymptomatic Trichomonas vaginalis infection.* N Engl J Med, 2001. **345**(7): p. 487-93.

199. Odendaal, H.J., et al., *Preterm labour--is bacterial vaginosis involved?* S Afr Med J, 2002. **92**(3): p. 231-4.

200. Andrews, W.W., et al., *Randomized clinical trial of metronidazole plus erythromycin to prevent spontaneous preterm delivery in fetal fibronectin-positive women.* Obstet Gynecol, 2003. **101**(5 Pt 1): p. 847-55.

201. Shennan, A., et al., *A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervicovaginal fetal fibronectin: the PREMET Study.* BJOG, 2006. **113**(1): p. 65-74.

202. McGregor, J.A., J.I. French, and K. Seo, *Adjunctive clindamycin therapy for preterm labor: results of a double-blind, placebo-controlled trial.* Am J Obstet Gynecol, 1991. **165**(4 Pt 1): p. 867-75.

203. Klebanoff, M.A., et al., *Is bacterial vaginosis a stronger risk factor for preterm birth when it is diagnosed earlier in gestation?* Am J Obstet Gynecol, 2005. **192**(2): p. 470-7.
204. Kurkinen-Raty, M., et al., *A randomised controlled trial of vaginal clindamycin for early pregnancy bacterial vaginosis.* BJOG, 2000. **107**(11): p. 1427-32.
205. Kekki, M., et al., *Vaginal clindamycin in preventing preterm birth and peripartal infections in asymptomatic women with bacterial vaginosis: a randomized, controlled trial.* Obstet Gynecol, 2001. **97**(5 Pt 1): p. 643-8.
206. Ugwumadu, A., et al., *Effect of early oral clindamycin on late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: a randomised controlled trial.* Lancet, 2003. **361**(9362): p. 983-8.
207. Okun, N., K.A. Gronau, and M.E. Hannah, *Antibiotics for bacterial vaginosis or Trichomonas vaginalis in pregnancy: a systematic review.* Obstet Gynecol, 2005. **105**(4): p. 857-68.
208. King, J. and V. Flenady, *Prophylactic antibiotics for inhibiting preterm labour with intact membranes.* Cochrane Database Syst Rev, 2002(4): p. CD000246.
209. Kenyon, S., M. Boulvain, and J.P. Neilson, *Antibiotics for preterm rupture of membranes.* Cochrane Database Syst Rev, 2010(8): p. CD001058.
210. Larsen, H., et al., *Birth outcome and risk of neonatal hypoglycaemia following in utero exposure to pivmecillinam: a population-based cohort study with 414 exposed pregnancies.* Scand J Infect Dis, 2001. **33**(6): p. 439-44.
211. Vinther Skriver, M., et al., *Pivmecillinam and adverse birth and neonatal outcomes: a population-based cohort study.* Scand J Infect Dis, 2004. **36**(10): p. 733-7.

212. Dencker, B.B., et al., *Birth outcome of 1886 pregnancies after exposure to phenoxymethylpenicillin in utero.* Clin Microbiol Infect, 2002. **8**(4): p. 196-201.
213. Benyamini, L., et al., *The safety of amoxicillin/clavulanic acid and cefuroxime during lactation.* Ther Drug Monit, 2005. **27**(4): p. 499-502.
214. Sorensen, H.T., et al., *Risk of malformations and other outcomes in children exposed to fluconazole in utero.* Br J Clin Pharmacol, 1999. **48**(2): p. 234-8.
215. De Santis, M., et al., *First-trimester itraconazole exposure and pregnancy outcome: a prospective cohort study of women contacting teratology information services in Italy.* Drug Saf, 2009. **32**(3): p. 239-44.
216. Wogelius, P., et al., *Further analysis of the risk of adverse birth outcome after maternal use of fluoroquinolones.* Int J Antimicrob Agents, 2005. **26**(4): p. 323-6.
217. Bar-Oz, B., et al., *The safety of quinolones--a meta-analysis of pregnancy outcomes.* Eur J Obstet Gynecol Reprod Biol, 2009. **143**(2): p. 75-8.
218. Rahangdale, L., et al., *An observational cohort study of Chlamydia trachomatis treatment in pregnancy.* Sex Transm Dis, 2006. **33**(2): p. 106-10.
219. Diav-Citrin, O., et al., *Pregnancy outcome after gestational exposure to mebendazole: a prospective controlled cohort study.* Am J Obstet Gynecol, 2003. **188**(1): p. 282-5.
220. Anderson, B.L., et al., *Additional antibiotic use and preterm birth among bacteriuric and nonbacteriuric pregnant women.* Int J Gynaecol Obstet, 2008. **102**(2): p. 141-5.
221. Simcox, R., et al., *Prophylactic antibiotics for the prevention of preterm birth in women at risk: a meta-analysis.* Aust N Z J Obstet Gynaecol, 2007. **47**(5): p. 368-77.

222. Lamont, R.F., *Can antibiotics prevent preterm birth--the pro and con debate.* BJOG, 2005. **112 Suppl 1**: p. 67-73.
223. Klein, L.L. and R.S. Gibbs, *Use of microbial cultures and antibiotics in the prevention of infection-associated preterm birth.* Am J Obstet Gynecol, 2004. **190**(6): p. 1493-502.
224. Bujold, E. and A.M. Morency, *Antibiotics for the prevention of preterm birth.* Aust N Z J Obstet Gynaecol, 2008. **48**(1): p. 124-5.
225. Lee, P.A., et al., *International Small for Gestational Age Advisory Board consensus development conference statement: management of short children born small for gestational age, April 24-October 1, 2001.* Pediatrics, 2003. **111**(6 Pt 1): p. 1253-61.
226. McCowan, L.M., et al., *Spontaneous preterm birth and small for gestational age infants in women who stop smoking early in pregnancy: prospective cohort study.* BMJ, 2009. **338**: p. b1081.
227. Shah, P.S., *Paternal factors and low birthweight, preterm, and small for gestational age births: a systematic review.* Am J Obstet Gynecol, 2010. **202**(2): p. 103-23.
228. Groom, K.M., et al., *Small-for-gestational-age infants classified by customized or population birthweight centiles: impact of gestational age at delivery.* Am J Obstet Gynecol, 2007. **197**(3): p. 239 e1-5.
229. Rizzo, G. and D. Arduini, *Intrauterine growth restriction: diagnosis and management. A review.* Minerva Ginecol, 2009. **61**(5): p. 411-20.
230. Saenger, P., et al., *Small for gestational age: short stature and beyond.* Endocr Rev, 2007. **28**(2): p. 219-51.
231. McCowan, L. and R.P. Horgan, *Risk factors for small for gestational age infants.* Best Pract Res Clin Obstet Gynaecol, 2009. **23**(6): p. 779-93.
232. Kleijer, M.E., G.A. Dekker, and A.R. Heard, *Risk factors for intrauterine growth restriction in a socio-economically disadvantaged region.* J Matern Fetal Neonatal Med, 2005. **18**(1): p. 23-30.

233. Odibo, A.O., et al., *Advanced maternal age is an independent risk factor for intrauterine growth restriction.* Am J Perinatol, 2006. **23**(5): p. 325-8.

234. Grivell, R., J. Dodd, and J. Robinson, *The prevention and treatment of intrauterine growth restriction.* Best Pract Res Clin Obstet Gynaecol, 2009. **23**(6): p. 795-807.

235. Bernstein, I.M., et al., *Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford Network.* Am J Obstet Gynecol, 2000. **182**(1 Pt 1): p. 198-206.

236. Low, J.A., et al., *Association of intrauterine fetal growth retardation and learning deficits at age 9 to 11 years.* Am J Obstet Gynecol, 1992. **167**(6): p. 1499-505.

237. Paz, I., et al., *The cognitive outcome of full-term small for gestational age infants at late adolescence.* Obstet Gynecol, 1995. **85**(3): p. 452-6.

238. Hales, C.N., et al., *Fetal and infant growth and impaired glucose tolerance at age 64.* BMJ, 1991. **303**(6809): p. 1019-22.

239. Ibanez, L. and F. de Zegher, *Puberty after prenatal growth restraint.* Horm Res, 2006. **65 Suppl 3**: p. 112-5.

240. Ibanez, L., et al., *Reduced ovulation rate in adolescent girls born small for gestational age.* J Clin Endocrinol Metab, 2002. **87**(7): p. 3391-3.

241. Larroque, B., et al., *School difficulties in 20-year-olds who were born small for gestational age at term in a regional cohort study.* Pediatrics, 2001. **108**(1): p. 111-5.

242. Leger, J., et al., *Reduced final height and indications for insulin resistance in 20 year olds born small for gestational age: regional cohort study.* BMJ, 1997. **315**(7104): p. 341-7.

243. Maulik, D., *Fetal growth restriction: the etiology.* Clin Obstet Gynecol, 2006. **49**(2): p. 228-35.

244. Hendrix, N. and V. Berghella, *Non-placental causes of intrauterine growth restriction.* Semin Perinatol, 2008. **32**(3): p. 161-5.

245. Scott, A., V. Moar, and M. Ounsted, *The relative contributions of different maternal factors in small-for-gestational-age pregnancies.* Eur J Obstet Gynecol Reprod Biol, 1981. **12**(3): p. 157-65.
246. Brown, Z.A., et al., *Effects on infants of a first episode of genital herpes during pregnancy.* N Engl J Med, 1987. **317**(20): p. 1246-51.
247. Bernstein, P.S. and M.Y. Divon, *Etiologies of fetal growth restriction.* Clin Obstet Gynecol, 1997. **40**(4): p. 723-9.
248. Rogerson, S.J., G.E. Grau, and N.H. Hunt, *The microcirculation in severe malaria.* Microcirculation, 2004. **11**(7): p. 559-76.
249. Goldenberg, R.L., et al., *The HPTN 024 Study: the efficacy of antibiotics to prevent chorioamnionitis and preterm birth.* Am J Obstet Gynecol, 2006. **194**(3): p. 650-61.
250. Lin, H.C. and S.F. Chen, *Increased risk of low birthweight and small for gestational age infants among women with tuberculosis.* BJOG, 2010. **117**(5): p. 585-90.
251. Sather, M., et al., *Global report on preterm birth and stillbirth (5 of 7): advocacy barriers and opportunities.* BMC Pregnancy Childbirth, 2010. **10 Suppl 1**: p. S5.
252. Ugwumadu, A., et al., *Oral clindamycin and histologic chorioamnionitis in women with abnormal vaginal flora.* Obstet Gynecol, 2006. **107**(4): p. 863-8.
253. Smaill, F., *Antibiotics for asymptomatic bacteriuria in pregnancy.* Cochrane Database Syst Rev, 2001(2): p. CD000490.
254. Smaill, F. and J.C. Vazquez, *Antibiotics for asymptomatic bacteriuria in pregnancy.* Cochrane Database Syst Rev, 2007(2): p. CD000490.
255. Organization, W.H., *International Classification of Diseases, Ninth Revision (ICD-9)*. 1977: Geneva, Switzerland.
256. sociaux, M.d.l.S.e.d.S., *Statistiques Annuelles de la Regie de l'assurance maladie du Quebec*. 1997, Government of Quebec: Quebec.

257. Berard, A. and A. Lacasse, *Validity of perinatal pharmacoepidemiologic studies using data from the RAMQ administrative database.* Can J Clin Pharmacol, 2009. **16**(2): p. e360-9.

258. Romero, R., et al., *Amniotic fluid interleukin 6 in preterm labor. Association with infection.* J Clin Invest, 1990. **85**(5): p. 1392-400.

259. Tamblyn, R., et al., *The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec.* J Clin Epidemiol, 1995. **48**(8): p. 999-1009.

260. Vilain, A., et al., *Agreement between administrative databases and medical charts for pregnancy-related variables among asthmatic women.* Pharmacoepidemiol Drug Saf, 2008. **17**(4): p. 345-53.

261. Bergman, U., *The history of the Drug Utilization Research Group in Europe.* Pharmacoepidemiol Drug Saf, 2006. **15**(2): p. 95-8.

262. Sultana, R., et al., *Outcomes in multiple gestation pregnancies among Canadian women age 35 years and older.* Healthc Q, 2011. **14**(4): p. 22-4.

263. Kramer, M.S., et al., *A new and improved population-based Canadian reference for birth weight for gestational age.* Pediatrics, 2001. **108**(2): p. E35.

264. Etminan, M. and A. Samii, *Pharmacoepidemiology I: a review of pharmacoepidemiologic study designs.* Pharmacotherapy, 2004. **24**(8): p. 964-9.

265. Morgan, S.R., C; Mooney, D; Martin, D, *The Canadian Rx Atlas*. December 2008, UBC Centre for Health Services and Policy Research: Vancouver, BC. p. 151.

266. Wise, R.A., A.J. Polito, and V. Krishnan, *Respiratory physiologic changes in pregnancy.* Immunol Allergy Clin North Am, 2006. **26**(1): p. 1-12.

267. Pitsouni, E., et al., *Single-dose azithromycin versus erythromycin or amoxicillin for Chlamydia trachomatis infection during pregnancy: a meta-analysis of randomised controlled trials.* Int J Antimicrob Agents, 2007. **30**(3): p. 213-21.

268. Ray, J.G., *Can studies of harm be harmful?* CMAJ, 2008. **179**(12): p. 1243-4.

269. Harpe, S.E., *Using secondary data sources for pharmacoepidemiology and outcomes research.* Pharmacotherapy, 2009. **29**(2): p. 138-53.

270. Berard, A., H.R. Nakhai-Pour, and P. Broy, *Antidepressant use (during pregnancy) and miscarriage.* CMAJ, 2010. **182**(10): p. 1079.

271. Kulaga, S., et al., *Antiepileptic drug use during pregnancy: Perinatal outcomes.* Seizure, 2011.

272. Nakhai-Pour, H.R., et al., *Use of nonaspirin nonsteroidal anti-inflammatory drugs during pregnancy and the risk of spontaneous abortion.* CMAJ, 2011.

273. Nakhai-Pour, H.R., E. Rey, and A. Berard, *Antihypertensive medication use during pregnancy and the risk of major congenital malformations or small-for-gestational-age newborns.* Birth Defects Res B Dev Reprod Toxicol, 2010. **89**(2): p. 147-54.

274. Ramos, E., M. St-Andre, and A. Berard, *Association between antidepressant use during pregnancy and infants born small for gestational age.* Can J Psychiatry, 2010. **55**(10): p. 643-52.

275. Savitz, D.A., N. Dole, and A.H. Herring, *Methodologic issues in the design and analysis of epidemiologic studies of pregnancy outcome.* Stat Methods Med Res, 2006. **15**(2): p. 93-102.

276. Pocock, S.J. and D.R. Elbourne, *Randomized trials or observational tribulations?* N Engl J Med, 2000. **342**(25): p. 1907-9.

277. Verhamme, K. and M. Sturkenboom, *Study designs in paediatric pharmacoepidemiology.* Eur J Clin Pharmacol, 2011. **67 Suppl 1**: p. 67-74.

278. De Jong van den Berg, L.T., et al., *Improvement of drug exposure data in a registration of congenital anomalies. Pilot-study: pharmacist and mother as sources for drug exposure data during pregnancy. EuroMAP Group. Europen Medicine and Pregnancy Group.* Teratology, 1999. **60**(1): p. 33-6.

279. Rothman, K.G., S; Lash, TL, *Modern Epidemiology*. 3rd edition ed. 2008, Philadelphia, PA: Lippincott Williamns & Wilkins. 758.

280. Zhanel, G.G., et al., *Antibiotic resistance in Escherichia coli outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA).* Int J Antimicrob Agents, 2006. **27**(6): p. 468-75.

281. Saez, M., M.A. Barcelo, and G. Coll de Tuero, *A selection-bias free method to estimate the prevalence of hypertension from an administrative primary health care database in the Girona Health Region, Spain.* Comput Methods Programs Biomed, 2009. **93**(3): p. 228-40.

APPENDIX

APPENDIX I: Ethics committee approval certificate

Le 2 décembre 2002

Docteure Anick Bérard
Centre de recherche
Étage A, bloc 7

CENTRE
DE RECHERCHE
DE L'HÔPITAL
SAINTE-JUSTINE
Le centre hospitalier universitaire mère-enfant

Pour l'amour des enfants

OBJET : Projet de recherche intitulé : Predictors of new medication utilisation and medication termination during pregnancy : Effect on the mother and child.
Notre référence : protocole # 1740

Chère Docteure,

Les membres du Comité d'éthique de la recherche ont examiné votre projet cité en rubrique à leur réunion du 28 novembre dernier. Le projet est acceptable du point de vue scientifique et éthique. Il s'agit d'une étude de dossiers ne nécessitant aucun formulaire d'information et de consentement. Toutefois, les membres du Comité tiennent à obtenir la copie de l'autorisation de la Commission d'accès à l'information avant de pouvoir approuver le projet.

Nous aimerions vous lire à ce sujet avant le 15 février 2003.

Veuillez recevoir, Chère Docteure, l'expression de nos sentiments les meilleurs.

Jean-Marie Therrien, Ph.D., Ethicien
Président du Comité d'éthique de la recherche.

JMT/nb

Université de Montréal

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APPENDIX II: *Commission de l'acces a l'information* approval

Commission d'accès
à l'information
du Québec

Siège social
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Québec, le 5 avril 2004

Madame Anick Bérard
Centre de recherche
Hôpital Sainte-Justine
3175, Côte Sainte-Catherine
Montréal (Québec) H3T 1C5

N/Réf. : 04 02 16

Madame,

Nous avons bien reçu votre demande d'autorisation d'obtenir, pour votre étude portant sur les déterminants d'utilisation et d'arrêt de médicaments durant la grossesse et l'impact que cela aura sur la mère et le nouveau-né, communication de renseignements nominatifs détenus par la Régie de l'assurance maladie du Québec (RAMQ) et le ministère de la Santé et des Services sociaux (MSSS).

Après étude de cette demande et conformément à l'article 125 de la *Loi sur l'accès aux documents des organismes publics et sur la protection des renseignements personnels*, nous vous autorisons à recevoir du MSSS, de l'Institut de la statistique du Québec (ISQ) à titre de mandataire du MSSS et de la RAMQ les renseignements nominatifs suivants :

- **de la RAMQ**, pour chaque femme qui a eu au moins un code d'actes ou un diagnostic relié à la grossesse (liste à l'annexe 1) entre le 1er janvier 1998 et le 31 décembre 2002 et qui a été couverte par la RAMQ pour ses médicaments pendant les 12 mois qui ont précédé la date du premier code d'actes ou diagnostic relié à la grossesse et pendant les 6 mois qui ont suivi cette date, ainsi que pour tous les bébés nés de ces

femmes entre le 1er janvier 1998 et 1e 30 septembre 2003, les renseignements énumérés à l'annexe 2, et ce, pour la période entre le 1er janvier 1997 et le 31 décembre 2003;

Pour les fins de la recherche, la Commission comprend que la RAMQ transférera au MSSS les numéros d'assurance maladie (NAM) non brouillés et brouillés des femmes identifiées au paragraphe précédent et de leurs nouveau-nés.

- **du MSSS**, à partir du fichier Med-Echo, pour les femmes et les nouveau-nés pour lesquels un NAM non brouillé et un NAM brouillé ont été communiqués par la RAMQ, les renseignements énumérés à l'annexe 3, et ce, pour la période entre le 1er janvier 1997 et le 31 décembre 2003; seul le NAM brouillé sera transmis au chercheur;

  Pour les fins de la présente recherche, la Commission comprend que la RAMQ transférera également au mandataire du MSSS, soit l'ISQ, les NAM brouillés des femmes identifiées au paragraphe précédent et de leurs nouveau-nés ainsi que le nom et le prénom de la mère, la date de naissance de la mère et la date de naissance des bébés.

- **de l'ISQ**, à titre de mandataire du MSSS, à parti du Registre des évènements démographiques, pour les femmes et les nouveau-nés pour lesquels un NAM brouillé ainsi que le nom et le prénom de la mère, la date de naissance de la mère et la date de naissance des bébés ont été communiqués par la RAMQ, les renseignements énumérés à l'annexe 4, et ce, pour la période entre le 1er janvier 1997 et le 31 décembre 2003; seul le NAM brouillé sera transmis au chercheur.

Cette autorisation est cependant assortie des conditions suivantes que vous devez respecter :

- vous devez assurer la confidentialité des renseignements nominatifs que vous recevrez;

- vous devez faire signer un engagement à la confidentialité aux membres de l'équipe de recherche qui n'ont pas signé le formulaire de demande

d'autorisation et à toute autre personne qui s'ajoutera, par la suite, à cette équipe;

- vous devez utiliser les renseignements reçus uniquement pour cette recherche particulière;

- dans vos rapports, vous ne devez pas publier un renseignement permettant d'identifier un individu;

- vous ne devez pas communiquer un renseignement reçu à d'autres personnes que celles qui sont autorisées à le recevoir dans le cadre de cette recherche;

- vous devez détruire tous les renseignements reçus, énumérés en annexe, pour lesquels l'autorisation de la Commission vous est accordée, au plus tard le 30 septembre 2010.

Enfin, il est opportun de vous rappeler que la décision ultime de vous communiquer ou non ces renseignements nominatifs appartient toujours aux organismes détenteurs, en l'occurrence la RAMQ et le MSSS.

Veuillez agréer, Madame, l'expression de nos sentiments les meilleurs.

Le directeur général,

DM/LB/lp

Denis Morency

p.j. (4)

c.c. M. André-Gaétan Corneau, RAMQ
M^me^ Brigitte Morin, RAMQ
M. Claude Lamarre, MSSS
M^me^ Louise Légaré, MSSS
M^me^ Louise Harvey, ISQ
M^me^ Line Beauchesne, ISQ

APPENDIX III: Co-authors authorization

APPENDIX IV: Editors authorization