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ORIGINAL ARTICLE

Perinatal antibiotic exposure of neonates in Canada and associated risk factors: a population-based study

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Abstract

Objective: To describe neonatal antibiotic exposures occurring immediately before and after birth and their associated risk factors.

Methods: A retrospective review of the hospital charts of 449 mother–neonate pairs enrolled in the Canadian Healthy Infant Longitudinal Development national birth-cohort study was conducted at two tertiary hospitals and one rural hospital in Manitoba, Canada. The main outcome measures included the following: maternal and neonatal antibiotic use during the perinatal period; indications for antibiotic use, including suspected neonatal sepsis, maternal group B *Streptococcus* (GBS), premature rupture of membranes and caesarean-section; maternal health status, focusing on gestational hypertension, gestational diabetes, obesity and primigravida pregnancies.

Results: During the perinatal period, 45.0% of neonates were exposed to antibiotics. Intravenous penicillin G (17%) and cefazolin (16%) were the most commonly administered intrapartum antibiotics. Colonization with GBS was confirmed in 21.2% of women and treated with antibiotics in 86% of cases. Overweight women and women with hypertension were significantly more likely to receive intrapartum antibiotics for caesarean section or GBS prophylaxis. Antibiotic treatment of the neonate was highest following emergency caesarean section (12%) or unknown maternal GBS status (20%).

Conclusions: Neonates in Canada are routinely exposed to antibiotics during the perinatal period.

Keywords

Antibiotic, intrapartum, neonate, overweight, prophylaxis

History

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Introduction

With caesarean section delivery rates on the rise and up to 50% of women carrying Group B Streptococcus (GBS) in some populations [1,2], prophylactic antibiotic treatment has become a routine practice during the birthing process. According to the Society of Obstetricians and Gynecologists of Canada (SOGC) guidelines, women should receive antibiotics before emergent or elective caesarean section [3]. Although lower than the national average of 28.0%, the caesarean delivery rate in Manitoba has increased from 5.0% in 1971 to 19.9% in 2009 [4]. To reduce the risk of neonatal GBS disease, the SOGC recommends intrapartum treatment with intravenous penicillin G for women testing positive for GBS or with prelabour rupture of membranes (PROM) at term [5]. A 2007 Manitoba survey found that among 87% of obstetricians, only 66% of family physicians followed the SOGC guidelines for universal GBS screening and antibiotic prophylaxis [6]. Furthermore, routine antibiotic prophylaxis for PROM is not supported by a 2002 Cochrane review [7].

Maternal antibiotic prophylaxis leads to indirect neonatal exposure when antibiotics cross the placenta or are expressed in breast milk. Neonates may also receive antibiotics directly for suspected early-onset sepsis; a 2007 Canadian Paediatric Society position statement recommends that newborns with clinical signs of sepsis be given empirical antibiotic treatment as soon as possible, normally for at least 48 h until blood testing is complete [8].

Infant antibiotic use is a documented risk factor for childhood asthma, allergy and obesity, and infant gut microbiota aberrancies have been linked with these conditions [9,10]. While these associations have not been widely studied in newborns, significant gut microbiota disruption has been observed following perinatal antibiotic exposure [11,12].

Examining the short- and long-term impact of antibiotic exposure requires complete and accurate documentation of exposures, especially during critical periods of development in

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early life. The objective of this study was to describe direct and indirect perinatal antibiotic exposures to newborns in Manitoba hospitals, and associated indications and risk factors.

Methods

This was a retrospective chart review of 449 mother–neonate pairs enrolled in the Canadian Healthy Infant Longitudinal Development (CHILD) national birth-cohort study, according to the following inclusion criteria: pregnancy in women aged 18 years or older with the ability to read and speak in English and birth at a minimum gestational age of 34 weeks and 4 d. Excluded were multiple-births, newborns with congenital abnormalities or those conceived by *in-vitro* fertilization (artificial insemination and hormonal therapy were acceptable) and infants who did not spend at least 80% of their nights in the household under study. Deliveries occurred at one rural and two urban hospitals in Manitoba, Canada.

Extracted from maternal and newborn birth records were data on the type, dose and timing of maternal and infant antibiotic exposure, indications for antibiotic treatment, maternal pre-pregnancy weight, maternal health status during pregnancy and mode of birth.

Type of caesarean section (emergent versus elective) was determined by the attending healthcare provider and recorded in the hospital chart. When type of caesarean section was not recorded, caesarean section with labour was classified as emergent, and caesarean section without labour was classified as elective. Maternal body mass index (BMI, in kg/m^2) was calculated from the standard provincial prenatal record form, a copy of which is typically included in the mother's hospital chart. The pre-pregnancy weight was used if available or a weight recorded no later than 20 weeks gestation. Following Health Canada guidelines [13], obesity was defined as a BMI over 30 kg/m^2, and overweight as BMI 25–30 kg/m^2. Maternal diabetes was defined as a positive diagnosis of type I, type II or gestational diabetes mellitus. Maternal hypertension was recorded in women with elevated blood pressure during the pregnancy, including women with essential and gestational hypertension. Maternal diabetes and gestational hypertension were documented from hospital records as diagnosed by a clinician during the pregnancy. Associations between antibiotic exposure and maternal health status were assessed by chi-squared test or logistic regression.

Results

Perinatal antibiotic exposures

A total of 202 neonates (45.0%) were exposed to antibiotics either directly or indirectly. Of these, 177 (39.4%) were exposed indirectly *via* the mother, 8 (1.8%) were directly exposed and 17 (3.8%) were both directly and indirectly exposed. Over 40% of mothers received antibiotics (194/449, 43.2%), with the majority administered intrapartum. Intravenous penicillin G was the most commonly administered antibiotic prior to delivery, with 77 mothers treated intrapartum (17.1%) and four treated post-delivery (0.9%) (Table 1). Treatment with cefazolin occurred in 76 mothers intrapartum (16.9%) and in 27 mothers post-delivery (6.0%), the latter being more common than treatment with penicillin.

Table 1. Type of antibiotics administered to mothers and neonates ($N = 449$).

	Indirect neonatal exposure				Direct exposure	
	Administered to mothers intrapartum		Administered to mothers post-delivery		Administered to neonates	
Antibiotic	*n*	%	*n*	%	*n*	%
Amoxicillin	2	0.4%	–	–	–	–
Ampicillin	15	3.3%	1	0.2%	23	5.1%
Cefazolin	76	16.9%	27	6.0%	1	0.2%
Cefoxitin	6	1.3%	6	1.3%	–	–
Cephalexin	1	0.2%	7	1.6%	1	0.2%
Clindamycin	10	2.2%	3	0.7%	–	–
Erythromycin	3	0.7%	–	–	–	–
Gentamicin	–	–	1	0.2%	24	5.3%
Metronidazole	–	–	4	0.9%	–	–
Mupirocin	1	0.2%	–	–	–	–
Penicillin G	77	17.1%	4	0.9%	–	–
Vancomycin	–	–	–	–	1	0.2%
Any antibiotics	176	39.2%	43	9.6%	25	5.6%
No antibiotics	273	60.8%	406	90.4%	424	94.4%

Other antibiotics administered to mothers, representing indirect exposure for neonates, included ampicillin, erythromycin, cephalexin, clindamycin, gentamicin and metronidazole. Twenty-five of the 449 neonates (5.6%) were directly exposed to antibiotics during the perinatal period, most commonly gentamicin (5.3%) and ampicillin (5.1%) (Table 1).

Indications for perinatal antibiotic exposure

The main indication for direct antibiotic treatment of neonates was suspected sepsis. Direct exposure occurred in 4.5% of vaginally-delivered infants, compared to 5.1% of infants delivered by elective caesarean section and 12.2% of those delivered by emergency caesarean section (Table 2).

Caesarean section (elective or emergent) was a major indication for maternal antibiotic treatment. Of the 449 mothers, 96 (21.4%) delivered by caesarean section; 39 (8.7%) were elective and 57 (12.7%) were emergent (Table 2). Of the mothers delivering *via* emergent caesarean section, 56/57 (98.3%) received antibiotics including 48 (84.2%) treated intrapartum and 23 (40.4%) treated post-delivery. Of the mothers delivering *via* elective caesarean section, 38/39 (97.4%) received antibiotics including 34 (87.2%) treated intrapartum and 5 (12.8%) treated post-delivery. Cefazolin was the agent of choice. Eight women (1.8%) received cefoxitin prophylaxis, of which four received doses before and after delivery, two prior to delivery and two post-delivery. The cefoxitin prophylaxis regimen was primarily administered at one hospital.

Other major indications for maternal antibiotic treatment, aside from caesarean section prophylaxis, included positive culture test for GBS and PROM greater than 18 h before labour (Table 2). Of the GBS-positive women who did not have PROM or a caesarean section delivery, 57/66 (86.4%) received antibiotic treatment, most commonly with intrapartum penicillin G. In a minority of cases, GBS-positive mothers either continued antibiotics ordered pre-delivery or started a new course of antibiotics. Four of 10 women (40%) with unknown GBS status and no other indication also

Table 2. Major indications for antibiotic treatment of mothers and neonates.

	Prevalence [$N = 449$]		Mother received antibiotic		Mother received antibiotic intrapartum		Mother received antibiotic post-delivery		Neonate received antibiotic	
Indication	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Birth Mode										
Vaginal	354	78.8%	101	28.5%	94	26.6%	16	4.5%	16	4.5%
Elective CS	39	8.7%	38	97.4%	34	87.2%	5	12.8%	2	5.1%
Emergent CS	57	12.7%	56	98.3%	48	84.2%	23	40.4%	7	12.2%
Group B Streptococcus*										
Unknown (excludes CS, PROM)	35 (10)	7.8%	4	40.0%	4	40.0%	1	10.0%	2	20.0%
Negative (excludes CS, PROM)	319 (222)	71.0%	14	6.3%	9	4.1%	9	4.1%	5	2.3%
Positive (excludes CS, PROM)	95 (66)	21.2%	57	86.4%	57	86.4%	3	4.6%	3	4.6%
Prelabour rupture of membranes*										
No (excludes CS, GBS)	376 (222)	83.7%	14	6.3%	9	4.1%	9	4.1%	5	2.3%
Yes (excludes CS, GBS)	73 (42)	16.3%	13	31.0%	13	31.0%	1	2.4%	1	2.4%
Number of indications (caesarean-section, GBS positive, and PROM alone)										
0 or Other	232	51.7%	18	7.8%	13	5.6%	10	4.3%	7	3.0%
1	176	39.2%	136	77.3%	125	71.0%	23	13.1%	10	5.7%
2	36	8.0%	35	97.2%	33	91.7%	7	19.4%	8	22.0%
3	5	1.1%	5	100%	5	100%	3	60.0%	0	–

CS, caesarean section; GBS, Group B Streptococcus; PROM, prelabour rupture of membranes.
*Calculation of treatment rates (percentages) for GBS and PROM exclude mothers with multiple indications for antibiotic treatment (denominator in parentheses).

received a course of antibiotics. In the absence of GBS colonization or caesarean section birth, intrapartum antibiotics were administered to 13/42 (31%) of women with PROM. Antibiotic treatment of the newborn was highest following emergency caesarean section (12.2%) or unknown maternal GBS status (20.0%).

Overall, 48% of women delivered by caesarean section, tested positive for GBS or had PROM (Table 2). Compared to women with none of these indications, who were treated at a rate of 5.6%, 71% of women with one indication received intrapartum antibiotics. Intrapartum antibiotic utilization was 91.7% among women with a second indication, and close to 20% received antibiotics following delivery. Five women had all three major indications, and all five received intrapartum antibiotics. The risk for direct antibiotic exposure increased to 22% among neonates born to women with multiple indications.

Maternal pregnancy history and health status

Over one-third of women (38.5%) were primigravida; hypertension (essential or gestational hypertension) was diagnosed in 8.2% of women and diabetes was present in 4.9% (Table 3). Nulliparity and hypertension, but not diabetes, were associated with maternal intrapartum antibiotic treatment. These associations were independent of each other, as follows: hypertension OR = 2.19 (95% CI: 1.10–4.36) and nulliparity OR = 1.72 (95% CI: 1.15–2.58). None of these conditions significantly increased risk for neonatal antibiotic treatment, although neonates born to diabetic mothers tended to receive antibiotics more often. Sixty-one percent of women with hypertension received chemoprophylaxis for caesarean section, and in 39%, antibiotics were administered subsequent to a positive culture for GBS. The distribution of indications for intrapartum antibiotic use in primigravida women was: 47% for GBS, 43% for caesarean chemoprophylaxis and 32% for PROM. Only 8% of nulliparous women had another infectious disease or unknown indication.

Of the 337 women with available weight data (Table 3), 28.5% were overweight and 22.0% were obese during pregnancy. The frequency of treatment with intrapartum antibiotics was positively correlated with the extent of pregnancy overweight in women, with over half (51.4%) of obese women receiving antibiotics before delivery, compared to 42.7% of overweight women and 31.1% of normal weight women (p for trend = 0.002). Obese women were significantly more likely to require a caesarean section (29.7%) compared to non-obese women (18.3%) ($p = 0.03$). Among mothers delivering vaginally, 32.7% of obese and 32.9% of overweight women received intrapartum antibiotics compared to 19.9% of their normal weight counterparts. The indication for antibiotic treatment during a vaginal delivery was a positive GBS culture in 74% of overweight or obese women, and PROM in 21% of these women.

Discussion

Main findings

Our population-representative study of 449 Manitoban mother–neonate pairs found that almost 40% of neonates were exposed to antibiotics indirectly during the perinatal period, and 6% were exposed directly. Indirect antibiotic exposure from intrapartum maternal treatment approached 90% among newborns born by caesarean or to mothers with GBS and was 31% among those born following PROM.

Strengths and limitations

Strengths of this study include the relatively large, population-based sample and the detailed review of hospital records. Limitations mainly relate to missing data in the birth chart. Antibiotic prophylaxis was not recorded for two caesarean

Table 3. Antibiotic treatment of mothers and neonates according to maternal pregnancy history and health status.

	Prevalence		Mother received antibiotic			Mother received antibiotic intrapartum			Mother received antibiotic post-delivery			Neonate received antibiotic		
	n	%	*n*	%	*p*	*n*	%	*p*	*N*	%	*p*	*n*	%	*p*
All mothers	449		194	43.2%		176	39.2%		43	9.6%		25	5.6%	
Primigravida pregnancy ($N = 418$)														
No	257	61.5%	99	38.5%	**0.01**	88	34.2%	**0.008**	21	8.2%	0.16	15	5.8%	0.92
Yes	161	38.5%	82	50.9%		76	47.2%		20	12.4%		9	5.6%	
Maternal pre-pregnancy weight ($N = 337$)*														
Normal	167	49.6%	62	37.1%	**0.02**	52	31.1%	**0.002**	17	10.2%	0.73	6	3.6%	0.14
Overweight	96	28.5%	43	44.8%		41	42.7%		8	8.3%		3	3.1%	
Obese	74	22.0%	40	54.1%		38	51.4%		7	9.5%		7	9.5%	
Maternal diabetes ($N = 449$)														
No	427	95.1%	182	42.6%	0.27	164	38.4%	0.13	42	9.8%	0.71†	22	5.2%	0.12†
Yes	22	4.9%	12	54.6%		12	54.6%		1	4.6%		3	13.6%	
Maternal hypertension ($N = 449$)														
No	412	91.8%	171	41.5%	**0.02**	155	37.6%	**0.02**	36	8.7%	**0.04**	22	5.3%	0.45*
Yes	37	8.2%	23	62.2%		21	56.8%		7	18.9%		3	8.1%	

Comparisons by chi-squared test, *Cochran-Armitage trend test, or †Fisher's Exact Test (due to small n); significant *p* values in **bold**.

deliveries despite being the standard of care in Canada. Furthermore, 112 women were missing weight data, which may have under-powered the analysis of pregnancy overweight and newborn antibiotic exposure.

Interpretation

The impact of hospital antibiotic exposures during the perinatal period is often overlooked by researchers evaluating the consequences of infant antibiotic use, since mothers may not accurately recall medications administered in hospital, and these medications are not captured by community-based prescription databases. In addition, the long-term consequences of perinatal antibiotic use may not be considered a priority, as these antibiotics are used to prevent immediate infection.

In our study population, the majority of neonatal antibiotic exposures occurred in the pre-delivery stage *via* maternal intravenous treatment. Penicillin G and cefazolin were the most commonly administered antibiotics. While both are minimally expressed in breast milk [14,15], a significant amount of penicillin and cefazolin will traverse the placenta [14,16]. A dose–response relationship between maternal antibiotics administered during pregnancy and risk for allergic disease in offspring has been reported from a UK general practice database, regardless of antibiotic type or trimester of administration [17].

The 2004 SOGC guidelines recommend universal screening for GBS at 35–37 weeks' gestation and intrapartum administration of antibiotics to prevent early-onset neonatal GBS disease [5]. In our study, 21% of pregnant women tested positive for GBS, the majority (86%) of which were treated with intravenous penicillin G intrapartum. A similar chemoprophylaxis rate was observed in the United States [18]. However, intravenous penicillin G is not the preferred choice in all countries, nor is universal screening. In a 2000 survey of obstetricians in Belgium, 32% never treated women with positive antenatal cultures for GBS, and oral amoxicillin (52%) was the drug of choice [19]. The United Kingdom's Royal College of Obstetricians and Gynaecologists recommends against routine screening for GBS carriage [20]. In Denmark, antibiotic prophylaxis for caesarean section is recommended, but unlike Canada, Denmark has adopted a non-culture based risk factor approach as opposed to universal GBS screening [21]. In the Danish COPSAC cohort, overall intrapartum antibiotic prevalence is 33%, with all women delivering via caesarean section receiving antibiotic prophylaxis and 13% of vaginal deliveries treated with intrapartum antibiotics [21]. We found intrapartum antibiotic use in Manitoba to be generally higher, with 27% of women delivering vaginally receiving antibiotics.

Following SOGC guidelines, close to 100% of women undergoing caesarean section in Manitoba hospitals received antibiotic prophylaxis, most often with cefazolin. However, 1.8% of women were treated with a second-generation cephalosporin, cefoxitin. While a 2010 Cochrane meta-analysis of caesarean section prophylaxis regimens found no differences in maternal infections following prophylaxis with first- or second-generation cephalosporins versus penicillins [22], first-generation cephalosporins are the preferred antibiotic in guidelines issued by the American College of Obstetricians and Gynaecologists (ACOG) and the SOGC [3,23]. At 11%, higher caesarean prophylaxis rates with second-generation cephalosporins have been reported in a recent survey of maternal–foetal specialists in the United States [24]. In keeping with SOGC and ACOG guidelines for women with penicillin allergy, some women in our study received clindamycin [3,23]. Finally, 85% of caesarean prophylactic antibiotics were administered prior to delivery, consistent with ACOG and SOGH guidelines, and at a much higher rate than currently reported in the United States [25].

Direct neonatal exposure to gentamicin and/or ampicillin over a 24–48 h period occurred in almost 6% of our cohort immediately after birth. Antibiotic use in the neonatal period is an independent risk factor for wheeze by 12 months of age [26], and use during the first six months is associated with subsequently increased body mass [27]. Direct or indirect neonatal exposure to extended-spectrum cephalosporins may further increase the risk of allergic disease and obesity [10,28].

Finally, our results show that maternal hypertension during pregnancy can elevate the likelihood for antibiotic exposure. Minassian et al. [29] recently reported an increased risk for pre-eclampsia following antibiotic use during the first two trimesters, proposing that infection may play a role in the pathogenesis of pre-eclampsia. Although caesarean section prophylaxis was the primary indication for women with hypertension in our study, over 30% were administered antibiotics for GBS. Consistent with the Danish study, we found an association between nulliparity and antibiotic use [21]. In addition, overweight women were more likely to receive intrapartum antibiotics than normal-weight women. Some of this utilization could be attributed to higher rates of caesarean section; however, maternal overweight also increased the risk of intrapartum antibiotic use in vaginal deliveries, where the primary indication was chemoprophylaxis for GBS. Manzanares et al. also observed greater GBS colonization in overweight mothers [30].

Neonates in Manitoba are routinely exposed to antibiotics during the perinatal period. Our results address the knowledge gap regarding in-hospital antibiotic exposure of newborns, data which are not recorded in community-based prescription databases or recalled by mothers in survey studies. Our ongoing research in the CHILD cohort will address the long-term consequences of the perinatal antibiotic exposures documented in this study. As we learn more about the impact of perinatal antibiotic exposure on the development of infant gut microbiota and immunity, options to reduce antibiotic exposure such as post-delivery prophylaxis for caesarean section and the adoption of non-culture risk factor algorithms for GBS, should be considered in Canada.

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This study was approved on 5 February 2008 by the University of Manitoba Health Research Ethics Board (protocol reference number H2007:255). Participants provided written informed consent upon enrolment in the CHILD study.

Declaration of interest

The authors declare no conflicts of interest.

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Author contributions

M. R. S. is principal investigator for the CHILD study; A. B. B. is the Winnipeg site leader and oversaw recruitment of study participants. A. L. K. conceived of the study design and oversaw data collection and analyses. R. R. P. conducted hospital chart reviews and drafted the manuscript. M. B. A. conducted statistical analyses. R. S. C. provided expertise on obstetric practice guidelines. All authors critically reviewed and approved the manuscript.

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