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Trends in using beta-blockers and methyldopa for hypertensive disorders during pregnancy in a Canadian population



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ABSTRACT

Objective: To describe trends in and patterns of antihypertensive drug use in a general obstetric population.

Study design: Historical cohort study. A total of 18,117 women who gave birth in a Saskatchewan hospital between January 1, 1980 and December 31, 2005 with a diagnosis of hypertensive disorders in pregnancy were identified and included in the analysis.

Results: The rate of treatment with antihypertensive drugs for pregnant women with chronic hypertension rose from 19.94% in 1980–1984 to 37.63% in 2000–2005. There were similar increases in antihypertensive drug use from 1.51% to 14.47% for gestational hypertension/non-severe preeclampsia, and from 1.56% to 20.86% for severe preeclampsia/eclampsia. Methyldopa was the most frequently used drug, followed by beta-blockers, with other antihypertensive drugs accounting for about 18.43% of total uses. The use of both methyldopa and labetalol has increased in recent years while the use of other antihypertensive drugs has decreased. Other antihypertensive drugs were more commonly prescribed in earlier gestation, while methyldopa and labetalol were generally prescribed in later gestation.

Conclusion: The use of antihypertensive drugs in pregnancy is relatively common and is increasing, with the liberal use of methyldopa and (especially) labetalol contributing appreciably to this increase.

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1. Introduction

Hypertensive disorders are common medical complications of pregnancy associated with significantly increased risks of maternal and neonatal complications [1]. Although the importance of early, aggressive blood pressure control outside pregnancy has been clearly demonstrated, the role of blood pressure control during

pregnancy remains unclear [2,3]. Even though treatment with antihypertensive drugs for severe hypertension in pregnancy (i.e., blood pressure > 160/110 mmHg) has been recommended, the question as to whether mild-to-moderately elevated blood pressure (i.e., blood pressure ≤ 160/110 mmHg) should be treated with antihypertensive drugs remains controversial [2,3]. Due to the lack of data on the efficacy and safety of antihypertensive drugs in pregnancy, there exist large variations in clinical practice guidelines among different countries/jurisdictions [2,3].

Alpha agonists (methyldopa) and beta-blockers (acebutolol, atenolol, labetalol, mepindolol, metoprolol, pindolol, oxprenolol, and propranolol) are among the most frequently recommended antihypertensive drugs in pregnancy, although other drugs such as

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calcium channel blockers (siradipine, nicardipine, nifedipine and verapamil), diuretics (hydrochlorothiazide, etc.), vasodilators (hydralazine and prazosin), ketanserin and glyceryltrinitrate have also been used [4–7]. The safety of beta-blockers (including labetalol) in pregnancy has not been well established, as some studies have reported an association between pregnancy exposure to beta-blockers and low birth weight infants [3,8,9]. The literature on the actual use of antihypertensive drugs in routine obstetric practice is sparse [10–13]. The objective of the present study was to assess trends and patterns of beta-blockers and methyldopa in pregnancy in general obstetric practice, using a population-based health care database in the Canadian province of Saskatchewan.

2. Materials and methods

Women who were eligible for coverage by the Saskatchewan Prescription Drug Plan (out-patient prescriptions) and who delivered a singleton in Saskatchewan from January 1, 1980 to June 30, 1987 or January 1, 1990 to December 31, 2005 with a diagnosis of a hypertensive disorder in pregnancy were identified through ICD-9/ICD-10-CA codes recorded in the database. Infants born between July 1, 1987 and December 31, 1989 were excluded because information on maternal drug use during pregnancy is incomplete. The majority of pregnant women with hypertensive disorders treated with antihypertensive drugs were treated with beta-blockers and/or methyldopa, and therefore we excluded women who were treated with other antihypertensive drugs alone. The following data were abstracted from the Saskatchewan health databases: a unique identifier, number of days between drug dispensing date and infant birth date, gestational age categories (0–23 weeks, 24–29 weeks, 30–37 weeks, 38–41 weeks, and more than 42 weeks), the specific name of beta-blockers and methyldopa, and women's demography. Information on prescription of antihypertensive drugs in pregnancy was ascertained for each study participant using number of days between drug dispensing date and infant birth date.

Hypertensive disorders in pregnancy are generally classified by professional guidelines as: pre-existing hypertension (chronic hypertension predating the pregnancy or when hypertension is diagnosed before 20 weeks' gestation); gestational hypertension (hypertension developing after 20 weeks' gestation and urinary

protein excretion < 0.3 g/day); preeclampsia (hypertension diagnosed after 20 weeks' gestation with urinary protein excretion > 0.3 g/day); and pre-existing hypertension with superimposed preeclampsia [1]. Eclampsia is a form of severe preeclampsia resulting in maternal seizure(s). These hypertensive disorders were captured by ICD-9 and ICD-10-CA codes contained in the database. For this study, we re-grouped the hypertensive disorders in pregnancy according to their severity and clinical management regimens. The classes were as follows: (1) chronic hypertension (women with chronic hypertension with or without superimposed preeclampsia); (2) gestational hypertension (women with either gestational hypertension or non-severe preeclampsia); and (3) severe preeclampsia (women with severe preeclampsia and/or eclampsia). For the rest of the paper these groups will be used.

We first described antihypertensive drug uses in pregnancy in the overall pregnancy and by trimesters. We then compared secular trends of treatment for the following three categories of antihypertensive drugs: (a) methyldopa, (b) labetalol, and (c) other beta-blockers. Supplementary analyses restricted to first pregnancies were also performed. All analyses were performed by SAS 9.2 (SAS Institute Inc., Cary, NC).

3. Results

A total of 19,003 pregnant women with a diagnosis of hypertensive disorders in pregnancy were identified from the database. Eight hundred and eighty-six women used other antihypertensive drugs alone without beta-blockers and/or methyldopa and were excluded, leaving 18,117 women for final analysis. Of them, 4229 had chronic hypertension, 13,006 had gestational hypertension/non-severe preeclampsia, and 882 had a diagnosis of severe preeclampsia.

Detailed information on specific antihypertensive drugs used in pregnancy is described in Table 1. Methyldopa was the most frequently used drug, followed by labetalol, with other beta-blockers the least used. About 18% women received other antihypertensive drugs along with beta-blockers and/or methyldopa.

Table 2 shows the use of antihypertensive drugs during different gestational periods. Methyldopa was the most frequently prescribed antihypertensive drug in the third trimester, followed by labetalol.

Table 1
Antihypertensive drug used in pregnant women by class of hypertensive disorders in Saskatchewan, 1980–2005.^a

Drug category	Overall n (%)	Chronic hypertension ^c n (%)	Gestational hypertension ^d n (%)	Severe preeclampsia ^e n (%)
Beta-blockers				
Acebutolol	17 (0.8)	16 (1.4)	1 (0.1)	0 (0.0)
Atenolol	171 (8.2)	139 (12.1)	25 (3.0)	7 (6.8)
Labetalol	449 (21.6)	221 (19.2)	187 (22.6)	41 (39.8)
Metoprolol	30 (1.4)	25 (2.2)	2 (0.2)	3 (2.9)
Nadolol	10 (0.5)	10 (0.9)	0 (0.0)	0 (0.0)
Oxprenolol	4 (0.2)	3 (0.3)	1 (0.1)	0 (0.0)
Pindolol	27 (1.3)	23 (2.0)	3 (0.4)	1 (1.0)
Propranolol	146 (7.0)	89 (7.7)	53 (6.4)	4 (3.9)
Timolol	19 (0.9)	15 (1.3)	4 (0.5)	0 (0.0)
Alpha-blockers				
Methyldopa	1404 (67.4)	766 (66.4)	581 (70.3)	57 (55.3)
Other antihypertensives ^b	384 (18.4)	337 (29.2)	40 (4.8)	7 (6.8)

^a Data between July 1, 1987 and December 31, 1989 were unavailable.

^b Along with beta-blockers and/or methyldopa.

^c Chronic hypertension: women with chronic hypertension with or without superimposed preeclampsia.

^d Gestational hypertension: women with either gestational hypertension or non-severe preeclampsia.

^e Severe preeclampsia: women with severe preeclampsia and/or eclampsia.

Table 2Categories of antihypertensive drugs used for hypertensive disorders in pregnancy by trimester in Saskatchewan, 1980–2005.^a

Drug category	First trimester (N=626) n (%)	Second trimester (N=849) n (%)	Third trimester (N=1820) n (%)
Labetalol	41 (6.6)	99 (11.7)	354 (19.5)
Other beta-blockers	144 (23.0)	135 (15.9)	172 (9.5)
Methyldopa	144 (23.0)	320 (37.7)	973 (53.5)
Other antihypertensives ^b	297 (47.4)	295 (34.8)	321 (17.6)

^a Data between July 1, 1987 and December 31, 1989 were unavailable.^b Along with beta-blockers and/or methyldopa.**Table 3**Categories of antihypertensive drug used for pregnant women with hypertensive disorders over time in Saskatchewan, 1980–2005.^a

Year	Chronic hypertension ^b				Gestational hypertension ^c				Severe preeclampsia ^d			
	N	Labetalol n (%)	Other beta-blockers n (%)	Methyldopa n (%)	N	Labetalol n (%)	Other beta-blockers n (%)	Methyldopa n (%)	N	Labetalol n (%)	Other beta-blockers n (%)	Methyldopa n (%)
1980–1984	617	0 (0.0)	64 (10.4)	68 (11.0)	3249	0 (0.0)	15 (0.5)	33 (1.0)	64	0 (0.0)	0 (0.0)	1 (1.6)
1985–June 87	434	1 (0.2)	50 (11.5)	52 (12.0)	1791	0 (0.0)	14 (0.8)	22 (1.2)	137	0 (0.0)	3 (2.2)	3 (2.2)
1990–1994	825	32 (3.9)	59 (7.2)	120 (14.6)	2929	15 (0.5)	21 (0.7)	93 (3.2)	178	1 (0.6)	1 (0.6)	5 (2.8)
1995–1999	1051	33 (3.1)	58 (5.5)	184 (17.5)	2438	25 (1.0)	20 (0.8)	196 (8.0)	153	3 (2.0)	4 (2.6)	10 (6.5)
2000–2005	1302	155 (11.9)	71 (5.5)	342 (26.3)	2599	147 (5.7)	16 (0.6)	237 (9.1)	350	37 (10.6)	6 (1.7)	38 (10.9)

^a Data between July 1, 1987 and December 31, 1989 were unavailable.^b Chronic hypertension: women with chronic hypertension with or without superimposed preeclampsia.^c Gestational hypertension: women with either gestational hypertension or non-severe preeclampsia.^d Severe preeclampsia: women with severe preeclampsia and/or eclampsia.

Table 3 compares secular trends of different categories of antihypertensive drugs. The use of both methyldopa and (especially) labetalol has increased in recent years, while the use of other beta-blockers has decreased.

Findings from supplementary analyses restricting to first pregnancies were similar (data available upon request).

4. Comment

Our large population-based study found that among pregnant women with a diagnosis of any hypertensive disorder, the overall treatment rate was 15.6% (of the 19,003 women with hypertensive disorders in pregnancy, 2,073 were dispensed beta-blockers and/or methyldopa plus 886 dispensed other antihypertensive drugs alone). Methyldopa was the most frequently used drug, followed by labetalol, with other beta-blockers the least used. The use of both methyldopa and (especially) labetalol has increased in recent years, while the use of other beta-blockers has decreased.

Our study was based on women with a diagnosis of hypertensive disorders in pregnancy in the majority of the obstetric population in the Canadian province of Saskatchewan, thereby reducing selection bias. Drug utilization information was abstracted from claim records. As a result, recall bias that might occur if the information was obtained directly from the women themselves can be avoided. Finally, the protracted study period permitted an assessment of the evolution of patterns of antihypertensive drug use during pregnancy over the course of more than two decades. These results provide novel and important information to health care providers and planners, as they can examine if similar trends/patterns exist in their own practices and jurisdictions.

Our study has several limitations. First, drugs dispensed during hospitalizations or given as samples in physicians' offices were not available from the Saskatchewan Prescription Drug Plan Database. These prescriptions should, however, represent only a

small fraction of antihypertensive medication use. Moreover, patients who received antihypertensive medication in hospitals or as samples in physicians' offices would be very likely to continue drug treatment, and thus later be identified using the drug the Saskatchewan Prescription Drug Plan Database. Second, there is no information on drug adherence in Saskatchewan's prescription drug file. As such, some patients who received prescription drugs from the pharmacy but did not actually consume the medications could be misclassified as "users", leading to an over-estimate of the prevalence of use. Finally, administrative health data are prone to certain degree of coding errors [14]. As a result, misclassifications of diseases and drugs could occur.

Our extensive search of the literature identified few articles reporting on the use of antihypertensive drugs in pregnancy. These articles revealed dramatically different rates of treatment, ranging from 96.4% for pregnant women with chronic hypertension in Hungary to 6.7% for pregnant women with gestational hypertension in our study [10–13] (Table 4). Considering only data from recent years (2000–2005), the overall treatment rate in our study population was quite similar to what was observed by Bateman et al. in the United States [13] but much lower than in the Hungarian population [10]. Different from our observation, the most common antihypertensive drugs dispensed during pregnancy in a HMO population in the United States observed by Andrade et al. were nifedipine (1219 deliveries; 1.0%), methyldopa (961 deliveries; 0.8%), atenolol (593 deliveries; 0.5%), and labetalol (576 deliveries; 0.5%) [12], suggesting that dramatic variation existed not only in overall treatment rate, but also in specific drugs used for treatment.

Bateman et al. also observed an increase in antihypertensive use during pregnancy from 3.5% in 2000 to 4.9% in 2007 [13], and attributed this to the increased rates of chronic hypertension and gestational hypertension in the population, which they considered as being secondary to increased obesity and advanced

Table 4
Prevalence of antihypertensive drug uses in pregnancy reported in the literature.

Author	Year of publication	Study population	Prevalence of antihypertensive drug uses in pregnancy (all pregnancies) (%)	Prevalence of antihypertensive drug uses in pregnancy (in pregnancies with hypertensive disorders) (%)
Bánhidly [10]	2010	Pregnant women with chronic hypertension in Hungary	N/A	96.4
Bánhidly [10]	2010	Pregnant women with gestational hypertension in Hungary	N/A	59.8
Anderson and Carr [11]	2008	Pregnant women in the United States	3.0	N/A
Andrade [12]	2008	Pregnant women in the United States	3.1	N/A
Bateman [13]	2012	Pregnant women in the United States	4.4	21.9 ^a
Xie (current study)	2013	Women with hypertensive disorders of pregnancy in Canada	N/A	15.6
Xie (current study)	2013	Pregnant women with chronic hypertension in Canada	N/A	27.1
Xie (current study)	2013	Pregnant women with gestational hypertension in Canada	N/A	6.7
Xie et al. (current study)	2013	Pregnant women with severe preeclampsia in Canada	N/A	8.6

N/A, not available.

^a Estimated by the formula: assuming 50% of the antihypertensive drugs were actually prescribed to women with a hypertensive disorders during pregnancy and further assuming that the rate of hypertensive disorders in pregnancy in the Medicaid population by Bateman et al. was 10%, the prevalence of antihypertensive drug uses in pregnant women with a diagnosis of hypertensive disorders during pregnancy is: $24,226 / (1,106,757 * 0.10) = 21.9\%$ in their cohort.

maternal age in the United States [15–17] during the study period. Both increased prevalence of hypertensive disorders of pregnancy caused by obesity and advanced maternal age and increased prescriptions for diagnosed hypertensive disorders may have led to increased maternal exposure to antihypertensive drugs. However, the magnitude of the increase caused by increased prescriptions observed in our study was much larger than the increase in prevalence of hypertensive disorders associated with increase in obesity and advanced maternal age [15–17]. Bateman et al. found that use of angiotensin-converting enzyme inhibitors, which are considered contraindicated in late pregnancy, occurred in 928 (4.9%) of antihypertensive medication users in the second trimester and in 383 (1.1%) women in the third trimester [13]. The use of contraindicated drugs in pregnancy is important to study, but we were unable to obtain direct information on certain types of drugs due to limitations with our dataset.

In summary, our population-based study found that, consistent with professional guidelines, the most frequently prescribed drugs were methyldopa and labetalol. Both can effectively control maternal blood pressure with no serious side effects [3]. However, there are still unresolved issues in the use of beta-blockers (including labetalol) in pregnancy, as several studies suggest that their use may be associated with low birth weight [3,8,9]. Antihypertensive drugs are often given to reduce maternal blood pressure in those with severe hypertension to prevent stroke and hypertensive crises [2,3]. There is, however, no conclusive evidence that antihypertensive treatment is beneficial to the mother in the case of mild-to-moderate hypertension in pregnancy. Given this uncertainty, the significantly increased use of labetalol for women with either chronic or gestational hypertension observed in our study deserves further attention. Large-scale epidemiologic studies should be conducted to assess the potential benefits and adverse effects of the commonly used antihypertensive drugs during pregnancy on mothers and fetuses.

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