Patterns of Outpatient Antihypertensive Medication Use During Pregnancy in a Medicaid Population

Brian T. Bateman, Sonia Hernandez-Diaz, Krista F. Huybrechts, Kristin Palmsten, Helen Mogun, Jeffrey L. Ecker, Michael A. Fischer

Abstract—Hypertensive disorders occur in approximately 6% to 8% of all pregnancies and are a significant source of maternal and fetal morbidity. Little is known about the range of agents routinely used in practice. We used Medicaid claims from 2000 to 2007 to identify completed pregnancies. We included women who were Medicaid beneficiaries from at least 3 months prior to last menstrual period to 1 month postdelivery, and were successfully linked to infant records. Maternal exposure to antihypertensive medications was derived from Medicaid pharmacy claim files, and duration of exposure was assigned based on the days' supply dispensed. We identified 1106757 Medicaid patients in our cohort, of whom 48453 (4.4%) were exposed to antihypertensive medications during pregnancy. The prevalence of antihypertensive use increased from 3.5% to 4.9% during the study period. Antihypertensive medication users were older than nonusers, more likely to be white or black, and more likely to have comorbid diabetes mellitus and renal disease. Overall, 1.9% of pregnant women were exposed during the first trimester, 1.7% during the second trimester, and 3.2% during the third trimester. The range of antihypertensive medications to which patients were exposed was highly heterogeneous and frequently included agents other than methyldopa or labetalol. Angiotensin-converting enzyme inhibitor exposure, which is contraindicated in late pregnancy, occurred in 928 (4.9%) antihypertensive medication users in the second trimester and 383 (1.1%) in the third trimester. Antihypertensive use during pregnancy is relatively common and increasing. The wide range of agents used during pregnancy includes medications considered contraindicated during pregnancy. (Hypertension. 2012;60:913-920.)

Key Words: hypertension ■ pregnancy ■ epidemiology ■ antihypertensives

Hypertensive disorders, including chronic hypertension, gestational hypertension, preeclampsia/eclampsia, and chronic hypertension with superimposed preeclampsia, occur in ≈6% to 8% of all pregnancies3,4 and are a significant source of maternal and fetal morbidity.5,6 For severe hypertension, pharmacological treatment is clearly indicated,3 but for mild-to-moderate hypertension, limited data are available. Synthesis of this information suggests that while treatment with medication decreases the risk of progression to severe hypertension, it has little effect on pregnancy outcomes including development of preeclampsia, preterm delivery, or fetal/neonatal demise.6 Antihypertensive exposure may confer some risk to the fetus by increasing rates of intrauterine growth restriction (although whether such associations are causal or confounded by indication or relative hypotension is unknown)7-9 and, for some agents, congenital malformations—although data are conflicting and these associations are controversial.6-15 Further, while methyldopa and labetalol are generally considered in guidelines as the first line/preferred agents for the treatment of hypertension in pregnancy,13-16 experts suggest that other antihypertensives can also be safely used.17-19

Little is known about how physicians balance these considerations in practice, or about the range of antihypertensive agents that physicians routinely use. Previous studies examining outpatient antihypertensive utilization in pregnancy had few data on Medicaid patients,20 which are important as Medicaid provides coverage for approximately 40% of all pregnancies in the United States.21 Earlier studies also did not examine patterns of management of patients taking antihypertensives prior to pregnancy or separately examine which agents are used in new initiators of antihypertensives in pregnancy.20 These data are important in focusing research efforts aimed at establishing the optimal approach to the treatment of patients with hypertensive disorders.

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To better understand these issues, we examined a cohort of pregnant patients enrolled in Medicaid from 2000 to 2007.

Methods

Definition of Cohort

Medicaid is the joint state and federal health insurance program for low-income individuals in the United States. The Medicaid Analytic eXtract (MAX) dataset contains individual-level Medicaid enrollment and Medicaid healthcare utilization claims, which includes inpatient, outpatient, and nonhospital pharmacy dispensing claims. MAX data were used to create a pregnancy cohort for studies of drug utilization and safety. The pregnancy cohort was identified from 2000 to 2007 MAX data. Women with an inpatient or outpatient delivery-related International Classification of Diseases, Ninth Revision (ICD-9) or Current Procedural Terminology codes were identified. These women were linked to infants by the Medicaid Case Number, which is typically shared by family members, and by matching an infant’s date of birth within a woman’s delivery date range. The delivery date range for women with inpatient deliveries was defined as the woman’s delivery admission and discharge dates and for women with outpatient deliveries it was defined as the 5 days before and after the delivery-related code date. After linkage and cleaning to eliminate apparent duplicate deliveries and incorrect linkages, 6,107,572 pregnancies were available. Because neither gestational length nor the date of the last menstrual period (LMP) are available in healthcare utilization data, the LMP was assigned to be 245 days before the delivery date for pregnancies that had ICD-9 codes indicative of preterm delivery, and as 270 days before the delivery date for all other pregnancies. This method has been validated and accurately classifies gestational length within 2 weeks for most deliveries.

Next, a number of eligibility criteria were applied to ensure that claims for women with pregnancies in the cohort would be present in MAX data. Abortions in which women were not continuously enrolled in Medicaid from 3 months before the month of the estimated LMP until the month after the delivery month were excluded. Also, pregnancies were excluded in which women had private insurance, restricted Medicaid benefits, or were enrolled in certain managed care plans in which claims were missing or underreported in MAX; 11,067,757 pregnancies remained in the cohort. The cohort included women from all states except Arizona, Connecticut, Michigan, and Montana. Approximately 50% of pregnancies in the cohort came from 6 states (California, Illinois, New York, Ohio, Tennessee, and Wisconsin).

Baseline Characteristics of the Cohort

Baseline characteristics of the cohort were determined and stratified by whether the patients were exposed to antihypertensives during pregnancy. The patients' age at the time of LMP and self-reported race, as documented in the Medicaid individual enrollment file, were extracted from the database. The presence of chronic hypertension, gestational hypertension, chronic renal disease, and multiple gestations was identified by the recording of the appropriate ICD-9 CM codes one or more times during any visit from 90 days prior to the LMP through delivery. Diabetes mellitus was defined by ICD-9 CM codes indicating pregestational diabetes mellitus or gestational diabetes mellitus or filled prescriptions for α-glucosidase inhibitors, glitazones, meglitinides, metformin, sulphonylureas, or insulin again from 90 days prior to the LMP through delivery. As a proxy for general health status and healthcare utilization, we also determined the number of physician visits for any reason and the number of distinct nonantihypertensive prescriptions drugs during the 90 days prior to the LMP. We also determined the mean age and distribution of race for the full, linked cohort.

Definition of Pregnancy Periods and Exposure

The prepregnancy period was defined as 90 days prior to the LMP to the day prior to the LMP. The first trimester was defined as the LMP through day 90 of pregnancy, second trimester as day 91 to day 180, and third trimester as day 181 to delivery.

We examined the outpatient use of antihypertensive treatments by therapeutic class, as shown in the online-only Data Supplement, based on pharmacy dispensing claims. The period of exposure to a medication for each woman was defined by the day the prescription was dispensed and the duration of the prescription based on days' supply. Antihypertensives dispensed prior to 90 days before the LMP were considered as an exposure if the days' supply extended into the defined prepregnancy period. The number of days supplied was accumulated for consecutive prescriptions of the same medication. Because dihydropyridines can be used off-label for the prevention or treatment of preterm labor and birth, we determined the proportion of patients with dihydropyridine exposure that had codes for preterm delivery or had diagnosis codes indicating preterm labor. We determined the number of women exposed to each class of antihypertensive in the prepregnancy period and each trimester, separately, as shown in Table 2.

Defining Patterns of Antihypertensive Utilization in Prepregnancy Users

For patients exposed to antihypertensive medications during the 90 days prior to the estimated LMP, we examined patterns of antihypertensive dispensing during the first trimester and second trimester. We determined for each class of antihypertensive used during the prepregnancy period, in a hierarchical fashion, the proportion of patients who continued on the prepregnancy class of medication, changed to methyldopa, changed to labetalol, changed to a different class (other than methyldopa or labetalol), and were not dispensed any antihypertensive during the first trimester (discontinuers).

Temporal Patterns of Utilization

For each year in the study period, we examined the proportion of women exposed to antihypertensives anytime during pregnancy and by trimester. We also examined trends in the exposure to the 4 most common antihypertensive classes at any time during pregnancy.

Results

There were 110,675 Medicaid patients included in our cohort of whom 48,453 (4.4%) were exposed to antihypertensive medications during pregnancy. Table 1 shows the baseline characteristics of the cohort, stratified by whether the woman was exposed to antihypertensives any time during pregnancy. In general, the antihypertensive exposed were older and more likely to be white or black. Over one fifth of the antihypertensive exposed also had pregestational or gestational diabetes mellitus and 3% had comorbid chronic renal disease. The antihypertensive exposed also had more nonantihypertensive medications prescribed prior to pregnancy and more prepregnancy physician visits. Compared with the full, linked cohort (n=6,107,572), the analytic cohort was slightly younger (23.2±5.8 versus 24.2±5.5 years old) and had a higher proportion of nonwhite women (60.1% versus 52.6%).

Table 2 shows the prevalence of exposure to antihypertensive medications in the 90 days before pregnancy and during each trimester. Overall, 2.0% (n=22,653) of the cohort was exposed prior to the estimated LMP, 1.9% (n=20,641) during the first trimester, 1.7% (n=19,000) during the second trimester, and 3.2% (n=35,571) during...
Table 1. Baseline Characteristics of Patients in the Medicaid Analytic Extract Pregnancy Cohort Stratified by Whether the Patients Were Exposed to Antihypertensives During Pregnancy

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Antihypertensive Exposed, N (%)</th>
<th>Antihypertensive Unexposed, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>48,453</td>
<td>1,058,304</td>
</tr>
<tr>
<td>Age at last menstrual period, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11–19</td>
<td>8,462 (17.5)</td>
<td>318,052 (30.1)</td>
</tr>
<tr>
<td>20–24</td>
<td>14,631 (30.2)</td>
<td>376,424 (35.6)</td>
</tr>
<tr>
<td>25–34</td>
<td>19,781 (40.8)</td>
<td>311,849 (29.5)</td>
</tr>
<tr>
<td>35–39</td>
<td>4,371 (9.0)</td>
<td>42,725 (4.0)</td>
</tr>
<tr>
<td>40–44</td>
<td>1,131 (2.3)</td>
<td>8,800 (0.8)</td>
</tr>
<tr>
<td>&gt;44</td>
<td>57 (0.1)</td>
<td>454 (&lt;0.1)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>21,598 (44.6)</td>
<td>41,926 (39.7)</td>
</tr>
<tr>
<td>Black</td>
<td>17,842 (36.8)</td>
<td>355,410 (33.6)</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>6,252 (13.0)</td>
<td>201,271 (19.1)</td>
</tr>
<tr>
<td>Native American</td>
<td>718 (1.5)</td>
<td>19,543 (1.9)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>994 (2.1)</td>
<td>37,563 (3.5)</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>1,049 (2.1)</td>
<td>24,591 (2.3)</td>
</tr>
<tr>
<td>Multiple gestations</td>
<td>2,162 (4.5)</td>
<td>19,172 (1.8)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregestational or gestational diabetes</td>
<td>10,994 (22.7)</td>
<td>103,023 (9.7)</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>1,439 (3.0)</td>
<td>12,335 (1.2)</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>15,190 (31.4)</td>
<td>19,821 (1.9)</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>3,569 (7.4)</td>
<td>32,589 (3.1)</td>
</tr>
<tr>
<td>Number of distinct nonantihypertensive prescription drugs (from 90 days prior to the LMP to LMP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>14,001 (28.9)</td>
<td>507,889 (48.0)</td>
</tr>
<tr>
<td>1 to 3</td>
<td>18,472 (38.1)</td>
<td>382,994 (36.2)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>15,980 (33.0)</td>
<td>167,421 (15.8)</td>
</tr>
<tr>
<td>Number of physician visits for any reason (from 90 days prior to the LMP to LMP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>18,281 (37.7)</td>
<td>563,312 (53.2)</td>
</tr>
<tr>
<td>1 to 3</td>
<td>21,926 (45.3)</td>
<td>411,868 (38.9)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>8,246 (17.0)</td>
<td>83,124 (7.9)</td>
</tr>
<tr>
<td>Exposed to antihypertensives prior to pregnancy</td>
<td>15,875 (32.8)</td>
<td>6,778 (0.6)</td>
</tr>
</tbody>
</table>

LMP indicates last menstrual period.

the third trimester. Prior to pregnancy, the most common medication classes were β blockers, thiazides, angiotensin-converting enzyme (ACE) inhibitors, dihydropyridines, and central α-antagonists. These were also the most common classes of exposure during the first trimester, although central α-antagonists accounted for a larger fraction of exposures in this group. By the second trimester, the proportion exposed to ACE inhibitors and thiazides declined substantially, whereas the proportion exposed to central –α-antagonists, combined α and β blockers, and dihydropyridines increased. In the third trimester, central –α-antagonists, combined α and β blockers, β blockers, and dihydropyridines accounted for most of the antihypertensive exposures. Of the dihydropyridine exposed, 14,905 (82.7%) had a diagnosis code indicating preterm labor or preterm delivery. Such medications are used off-label as tocolytics to attenuate preterm contractions.

In Table 3 shows the patterns of antihypertensive dispensing among initiators of antihypertensive therapy during each trimester; not exposed to antihypertensives at any point before or during pregnancy, prior to the period in question. The most commonly dispensed agents varied by trimester, but included central α-antagonists, β blockers, thiazides, calcium channel blockers, and combined α and β blockers.

In Figure 1A and 1B, we show patterns of antihypertensive dispensing during the first and second trimester, respectively, for patients taking antihypertensives prepregnancy stratified by class of prepregnancy therapy. For all classes of antihypertensives, during the first trimester, about half discontinued therapy (meaning no dispensing of medication during the trimester), about a third continued their prepregnancy medication, and the balance switched to methyldopa, labetalol, or another antihypertensive. By the second trimester between 50% and 70%, depending on the prepregnancy antihypertensive class, discontinued therapy. Also by this point in pregnancy, the majority of patients taking thiazides or ACE inhibitors prepregnancy, either discontinued therapy or were switched to methyldopa or labetalol. For those on β blockers or calcium channel blockers, an approximately equal proportion continued the prepregnancy class and switched to methyldopa or labetalol. Additional information on this analysis is available in the online-only Data Supplement. We also examined the overall proportion of women taking antihypertensives prior to pregnancy and found that 12,373 (54.6%) received no antihypertensive during the first trimester and 15,692 (69.3%) received no antihypertensive during the second trimester. When we restricted the analysis to patients who were coded as having a diagnosis of chronic hypertension, only 2722 (31.6%) received no antihypertensive in the first trimester and 3991 (46.4%) received no antihypertensive during the second trimester.

Figure 2 shows temporal trends in the exposure prevalence for antihypertensives anytime during pregnancy and by trimester from 2000 to 2006. Observations from deliveries in 2007 were not included due to concern that the small sample size from that year (n=29255) may generate unstable estimates. The prevalence of exposure at anytime during pregnancy increased from 3.5% in 2000 to 4.9% in 2006 and during the first trimester from 1.4% to 2.0%. Figure 3 shows trends in the prevalence of exposure at any point during pregnancy to the 4 most common classes. Increases were seen for all classes, but were most substantial for combined α and β blockers and dihydropyridines.

 Discussion

In this study of over 1.1 million Medicaid pregnancies, we found antihypertensive medications to be a common
pregnancy exposure whose prevalence is consistently increasing. From 2000 to 2006 alone, the prevalence of antihypertensive use both in the first trimester and in pregnancy overall increased nearly 50%; by 2006 nearly 5% of all pregnancies were exposed to antihypertensives. We also found that there is substantial heterogeneity in the range of antihypertensive agents used across all trimesters of pregnancy and in the approach to the management of patients entering pregnancy on antihypertensives.

Although professional guidelines generally recommend methyldopa and labetalol as the first-line treatments for hypertension in pregnancy,\textsuperscript{3,5,16} our data suggest that in actual practice the use of other agents is very common. A significant proportion of patients taking antihypertensives prior to pregnancy are maintained on their prepregnancy agent, and not switched to one of the preferred agents. Even for new initiators of antihypertensive therapy, β blockers, thiazides, and calcium channel blockers were frequently chosen. With the exception of methyldopa (which is category B), the Food and Drug Administration categorizes most antihypertensives as category C, which means that animal studies either show an adverse effect or are lacking and no well-controlled human studies exist.\textsuperscript{24} Concerns have been raised that β blockers can predispose to intrauterine growth restriction\textsuperscript{8} and neonatal hypoglycemia.\textsuperscript{14} Calcium channel blockers have recently been linked to increased rates of neonatal seizures.\textsuperscript{14} Diuretics have been shown to prevent normal plasma volume expansion in pregnancy,\textsuperscript{25} although it is unclear if this is detrimental. While experts interpret the limited data available to suggest the general safety of these agents during pregnancy,\textsuperscript{3,17,24} more work is needed to establish that this is the case and to verify and establish the magnitude of any risks that do exist. Further, there is virtually no data on the comparative effectiveness and safety of the different treatment options for hypertension.

### Table 2. Distribution of Antihypertensive Medications Before and During Pregnancy by Class Within Users of Antihypertensive Medications

<table>
<thead>
<tr>
<th>Antihypertensive Type</th>
<th>Prepregnancy, N(%)</th>
<th>First Trimester, N(%)</th>
<th>Second Trimester, N(%)</th>
<th>Third Trimester, N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>22 653</td>
<td>20 641</td>
<td>19 000</td>
<td>35 571</td>
</tr>
<tr>
<td>Diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazides</td>
<td>4234 (18.7)</td>
<td>3278 (15.9)</td>
<td>1074 (5.7)</td>
<td>665 (1.9)</td>
</tr>
<tr>
<td>Potassium-sparing agents</td>
<td>404 (1.8)</td>
<td>287 (1.4)</td>
<td>83 (0.4)</td>
<td>55 (0.2)</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>169 (0.7)</td>
<td>130 (0.6)</td>
<td>84 (0.4)</td>
<td>81 (0.2)</td>
</tr>
<tr>
<td>Adrenergic inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central α-antagonists</td>
<td>1992 (8.8)</td>
<td>5839 (28.3)</td>
<td>7921 (41.7)</td>
<td>9914 (27.9)</td>
</tr>
<tr>
<td>α Blockers</td>
<td>89 (0.4)</td>
<td>72 (0.3)</td>
<td>31 (0.2)</td>
<td>32 (0.1)</td>
</tr>
<tr>
<td>β Blockers</td>
<td>7354 (32.5)</td>
<td>6340 (30.7)</td>
<td>4238 (22.3)</td>
<td>3814 (10.7)</td>
</tr>
<tr>
<td>Combined α and β blockers</td>
<td>941 (4.2)</td>
<td>1793 (8.7)</td>
<td>2879 (15.2)</td>
<td>4426 (12.4)</td>
</tr>
<tr>
<td>Direct vasodilators</td>
<td>98 (0.4)</td>
<td>179 (0.9)</td>
<td>268 (1.4)</td>
<td>413 (1.2)</td>
</tr>
<tr>
<td>Calcium channel antagonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondihydropyridines</td>
<td>1322 (5.8)</td>
<td>1081 (5.2)</td>
<td>591 (3.1)</td>
<td>638 (1.8)</td>
</tr>
<tr>
<td>Dihydropyridines*</td>
<td>3192 (14.1)</td>
<td>2590 (12.5)</td>
<td>3766 (19.8)</td>
<td>18018 (50.7)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>3979 (17.6)</td>
<td>3280 (15.9)</td>
<td>928 (4.9)</td>
<td>383 (1.1)</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>798 (3.5)</td>
<td>666 (3.2)</td>
<td>189 (1)</td>
<td>87 (0.2)</td>
</tr>
<tr>
<td>Combination drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β Blockers and diuretics</td>
<td>312 (1.4)</td>
<td>270 (1.3)</td>
<td>88 (0.5)</td>
<td>48 (0.1)</td>
</tr>
<tr>
<td>ACE inhibitors and diuretics</td>
<td>512 (2.3)</td>
<td>424 (2.1)</td>
<td>106 (0.6)</td>
<td>48 (0.1)</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonists and diuretics</td>
<td>647 (2.9)</td>
<td>563 (2.7)</td>
<td>157 (0.8)</td>
<td>65 (0.2)</td>
</tr>
<tr>
<td>Calcium antagonists and ACE inhibitors</td>
<td>462 (2.0)</td>
<td>387 (1.9)</td>
<td>107 (0.6)</td>
<td>55 (0.2)</td>
</tr>
<tr>
<td>Other combinations</td>
<td>1758 (7.8)</td>
<td>1324 (6.4)</td>
<td>397 (2.1)</td>
<td>316 (0.9)</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme. The Medicaid Analytic Extract Pregnancy Cohort. Prepregnancy is defined as exposure from 90 days prior to the last menstrual period (LMP) to LMP. Pregnancy is defined as the LMP to day 270 for term deliveries and 245 for preterm deliveries. First trimester is defined as LMP to 90 days, second trimester as 91 days to 180 days, third trimester as 181 to delivery. *Dihydropyridines are used off-label for tocolysis and the prevention of preterm labor; 14 905 patients treated with these medications had preterm labor or preterm delivery.
Another important finding in our study is that approximately half of all patients taking antihypertensive agents prior to pregnancy discontinue treatment during the first or second trimester (Figure 1). Meta-analysis of the available data suggests that pharmacological therapy for mild-to-moderate hypertension decreases the incidence of severe hypertension, but does not reduce the risks of placental abruption, fetal demise, superimposed preeclampsia, or preterm birth (but the available data are underpowered to show even moderate reductions in these outcomes). Whether the decrease in severe maternal hypertension translates into decreased maternal morbidity also remains unclear. Again, further research is needed.

It is notable that in our large sample, several hundred women were exposed to ACE inhibitors or angiotensin II receptor blockers during late pregnancy. These agents are known to be fetotoxic in the second or third trimester (Figure 1). Although the circumstances of their use cannot be discerned in this administrative dataset, automatic refills in patients with late registration to prenatal care or prescribing physicians’ failure to ask about the possibility of pregnancy are two plausible explanations. This underscores the caution with which physicians must use fetotoxic agents in women of reproductive age. Unplanned pregnancy and late registration to prenatal care are not uncommon, particularly in disadvantaged populations such as those served by Medicaid. Automatic refills of potentially fetotoxic medications may be hazardous in these patients.

Although data are conflicting, there is also substantial concern about the teratogenic potential of ACE inhibitors and angiotensin II receptor blockers during the first trimester. In our sample, these agents accounted for nearly one fifth of antihypertensive exposures during the first trimester. As noted in the paragraph above, the precise circumstances of the use of these agents cannot be determined from claims data, but the prevalence of this exposure raises important safety concerns. Resolution of this controversy with larger and better controlled studies is necessary.

Consistent with what has been observed in other populations, we report a marked increase in utilization of antihypertensives in pregnancy during our study period. While clearly some of this increase is due to greater off-label use of dihydropyridines for the prevention and treatment of preterm labor, we also observe increases in other classes of medications, including centrally acting α antagonists, β blockers, and mixed α-β blockers. The heterogeneous nature of the agents used, suggest these data are urgently needed.

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Although data are conflicting, there is also substantial concern about the teratogenic potential of ACE inhibitors and angiotensin II receptor blockers during the first trimester. In our sample, these agents accounted for nearly one fifth of antihypertensive exposures during the first trimester. As noted in the paragraph above, the precise circumstances of the use of these agents cannot be determined from claims data, but the prevalence of this exposure raises important safety concerns. Resolution of this controversy with larger and better controlled studies is necessary.

Consistent with what has been observed in other populations, we report a marked increase in utilization of antihypertensives in pregnancy during our study period. While clearly some of this increase is due to greater off-label use of dihydropyridines for the prevention and treatment of preterm labor, we also observe increases in other classes of medications, including centrally acting α antagonists, β blockers, and mixed α-β blockers.
and β blockers. First trimester utilization of antihypertensives also rose dramatically. These findings are consistent with the rising rates of chronic hypertension and gestational hypertension observed in population-based studies,\textsuperscript{2,26} which in turn may reflect rising rates of obesity\textsuperscript{27} and advanced maternal age\textsuperscript{28} in US parturients.

It is notable that less than half of the patients exposed to antihypertensives in pregnancy had an inpatient or outpatient ICD-9 code for chronic or gestational hypertension. While this may be partially explained by the prescription of antihypertensives for other conditions, it likely primarily reflects the imperfect sensitivity of ICD-9 codes for hypertensive conditions in claims data.\textsuperscript{29–31} This suggests that utilization of medications along with diagnostic codes may provide a better approach to defining comorbidities in surveillance or epidemiological studies using claims data, than algorithms that rely on ICD 9 codes alone.

Our study is subject to certain limitations. To assure accurate estimation of gestational age and continuous enrollment from 3 months prior to pregnancy through delivery, we only included those women in the MAX cohort for whom a linkage to neonatal record is possible and who met our strict inclusion criteria. This resulted in a substantial reduction in the size of the cohort which may decrease its representativeness of the general Medicaid population. Indeed, our cohort is younger and has a larger proportion of nonwhite women than the cohort before exclusion based on eligibility. Our data only include those pregnancies that result in livebirths, such that antihypertensive exposures in pregnancies that result in other outcomes (stillbirths, elective terminations, and miscarriages) are not captured in the present analysis. Also, while the use of Medicaid pharmacy data provides information on medication dispensing which is not subject to recall bias, it does not provide information on whether the medication was actually
taken, which may result in misclassification. However, most Medicaid patients face at least nominal copayments for their prescriptions and these charges often represent a financial pressure for these low-income patients, suggesting that if the prescription is filled, it is likely taken. Additionally, as we only require 3 months of enrollment prior to pregnancy and examine this period to determine prepregnancy exposure to antihypertensives, this may result in a slight underestimate, as some patients may discontinue therapy >3 months prior to the LMP in anticipation of pregnancy. Likewise, the number of women exposed to antihypertensives during the prepregnancy window will be slightly underestimated due to women who were not Medicaid eligible >3 months before the LMP and were still taking antihypertensives dispensed prior to the window but did not refill their prescription during the window. Further, we do not have accurate information on the indications for the prescription of an antihypertensive medication, a large proportion of the dihydropyridine exposures in the third trimester are likely for off-label use for tocolysis. 32 There is significant heterogeneity in the range of agents used and the management of patients taking antihypertensives prior to pregnancy. Research investigating the comparative safety and efficacy of antihypertensive therapy in pregnancy is urgently needed to define the optimal approach to therapy.

**Sources of Funding**

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**Disclosures**

None.

**References**


Novelty and Significance

What Is New?

- This analysis includes over 1 million women enrolled in Medicaid to fill a gap in knowledge of population-level patterns of antihypertensive medication use during pregnancy.
- Antihypertensive exposure occurs in nearly 5% of pregnant women and is increasing in frequency. The range of treatments used is highly heterogeneous.
- Antihypertensives prescribed prior to pregnancy are frequently still being refilled into the first trimester and beyond, suggesting that exposure to potentially fetotoxic medications is not uncommon.

What Is Relevant?

- With increasing exposure to antihypertensive medications during pregnancy, this study identifies areas of concern for clinicians caring for these patients and establishes the need for further research to define the safety and efficacy of the available agents.

Summary

Antihypertensive use during pregnancy is relatively common and increasing. The wide range of agents used during pregnancy includes medications considered contraindicated during pregnancy. Data on the comparative safety and efficacy of specific antihypertensives in pregnant women are urgently needed.
Patterns of Outpatient Antihypertensive Medication Use During Pregnancy in a Medicaid Population

Brian T. Bateman, Sonia Hernandez-Diaz, Krista F. Huybrechts, Kristin Palmsten, Helen Mogun, Jeffrey L. Ecker and Michael A. Fischer

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1. Title: PATTERNS OF OUTPATIENT ANTIHYPERTENSIVE MEDICATION USE DURING PREGNANCY IN A MEDICAID POPULATION

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Fax: 617-232-8602

E-mail:  BBateman@partners.org
Antihypertensive Drugs, By Class

1. Diuretics
   a. Thiazides (TZDS)
      Bendroflumethiazide
      Benzthiazide
      Chlorothiazide
      Chlorothiazide Sodium
      Chlorthalidone
      Cyclothiazide
      Hydrochlorothiazide
      Hydroflumethiazide
      Indapamide
      Methyclothiazide
      Metolazone
      Polythiazide
      Quinethazone
      Trichlormethiazide

   b. Potassium-Sparing Agents (PSA)
      Amiloride Hydrochloride
      Spironolactone
      Triamterene

   c. Acetazolamide - (AZ)
Acetazolamide

2. Adrenergic Inhibitors
   a. Peripheral Agents (PA)
      Guanadrel Sulfate
      Guanethidine Sulfate
      Reserpine
   
   b. Central Alpha-Antagonists (CAA)
      Clonidine Hydrochloride
      Guanabenz Acetate
      Guanfacine Hydrochloride
      Methyldopa
      Methyldopate Hydrochloride
      Phenoxybenzamine Hydrochloride
      Phentolamine Hydrochloride
      Tolazoline Hydrochloride
   
   c. Alpha Blockers (AB)
      Doxazosin Mesylate
      Prazosin Hydrochloride
      Terazosin Hydrochloride
   
   d. Beta Blockers (BB)
      Acebutolol Hydrochloride
      Atenolol
      Betaxolol Hydrochloride
      Bisoprolol Fumarate
      Carteolol Hydrochloride
      Esmolol Hydrochloride
      Metoprolol Succinate
Metoprolol Tartrate
Nadolol
Penbutolol Sulfate
Pindolol
Propranolol Hydrochloride
Sotalol Hydrochloride
Timolol Maleate

e. Combined Alpha And Beta Blockers
Carvedilol
Labetalol Hydrochloride

3. Direct Vasodilators (VD)
Hydralazine Hydrochloride
Minoxidil

4. Calcium Channel Antagonists (CCB)
a. Nondihydropyridines
Diltiazem Hydrochloride
Diltiazem Malate
Mibefradil Di-Hydrochloride
Verapamil Hydrochloride

b. Dihydropyridines
Amlodipine Besylate
Bepridil Hydrochloride
Felodipine
Isradipine
Nicardipine Hydrochloride
Nifedipine
Nimodipine
Nisoldipine

5. ACE Inhibitors (ACEI)
   Benazepril Hydrochloride
   Captopril
   Enalapril Maleate
   Enalaprilat
   Enalaprilat Dihydrate
   Fosinopril Sodium
   Lisinopril
   Moexipril Hydrochloride
   Perindopril Erbumine
   Quinapril Hydrochloride
   Ramipril
   Trandolapril

6. Angiotensin II Receptor Blockers (ARB)
   Candesartan Cilexetil
   Eprosartan Mesylate
   Irbesartan
   Losartan Potassium
   Olmesartan Medoxomil
   Telmisartan
   Valsartan

7. Combination Drugs
   a. Beta Blockers And Diuretics
      Bendroflumethiazide/Nadolol
      Chlorthalidone/Atenolol
      Hydrochlorothiazide/Bisoprolol Fumarate
      Hydrochlorothiazide/Labetalol Hydrochloride
Hydrochlorothiazide/Metoprolol Tartrate
Hydrochlorothiazide/Propranolol
Hydrochlorothiazide/Propranolol Hydrochloride
Hydrochlorothiazide/Timolol

b. ACE Inhibitors And Diuretics
Benazepril Hydrochloride/Hydrochlorothiazide
Captopril/Hydrochlorothiazide
Enalapril Maleate/Hydrochlorothiazide
Fosinopril Sodium/Hydrochlorothiazide
Lisinopril/Hydrochlorothiazide
Moexipril Hydrochloride/Hydrochlorothiazide
Quinapril Hydrochloride/Hydrochlorothiazide

c. Angiotensin II Receptor Antagonists And Diuretics
Candesartan Cilexetil/Hydrochlorothiazide
Irbesartan/Hydrochlorothiazide
Losartan Potassium/Hydrochlorothiazide
Telmisartan/Hydrochlorothiazide
Valsartan/Hydrochlorothiazide

d. Calcium Antagonists And ACE Inhibitors
Benazepril Hydrochloride/Amlodipine Besylate
Enalapril Maleate/Diltazem Maleate
Enalapril Maleate/Felodipine
Trandolapril/Verapamil Hydrochloride

e. Other Combinations
Bendroflumethiazide/Potassium Chloride
Crypenamine/Methylclothiazide
Hydrochlorothiazide/Spironolactone
Spironolactone/Hydrochlorothiazide
Hydrochlorothiazide/Triamterene
Hydrochlorothiazide/Amiloride Hydrochloride
Clonidine Hydrochloride/Chlorthalidone
Deserpidine/Hydrochlorothiazide
Deserpidine/Methyclothiazide
Guanethidine Sulfate/Hydrochlorothiazide
Methyldopa/Chlorothiazide
Methyldopa/Hydrochlorothiazide
Reserpine/Benzthiazide
Reserpine/Chlorthalidone
Reserpine/Hydrochlorothiazide
Reserpine/Hydroflumethiazide
Reserpine/Methyclothiazide
Reserpine/Polythiazide
Reserpine/Quinethazone
Reserpine/Trichlormethiazide
Hydralazine Hydrochloride/Hydrochlorothiazide
Hydralazine Hydrochloride/Reserpine
Hydralazine Hydrochloride/Reserpine/Hydrochlorothiazide
Hydralazine/Reserpine/Hydrochlorothiazide
Hydralazine Hydrochloride/Hydrochlorothiazide
Prazosin Hydrochloride/Polythiazide
Methyclothiazide/Pargyline
Rauwolfia Serpentina/Bendroflumethiazide
Rauwolfia/Bendroflumethiazide/Potassium

8. Miscellaneous
Diazoxide
Metyrosine
Reserpine/Mannitol Hexanitrate
Table S1. Among patients taking antihypertensives prior to pregnancy, patterns of antihypertensive dispensing during the first trimester. The Medicaid Analytic Extract Pregnancy Cohort.

<table>
<thead>
<tr>
<th>Antihypertensive type</th>
<th>Continue same antihypertensive</th>
<th>No antihypertensive</th>
<th>Change to methyldopa</th>
<th>Change to labetalol</th>
<th>Change to other antihypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazides</td>
<td>1295 (30.59)</td>
<td>2104 (49.69)</td>
<td>422 (9.97)</td>
<td>112 (2.65)</td>
<td>301 (7.11)</td>
</tr>
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<td>Potassium-Sparing Agents</td>
<td>100 (24.75)</td>
<td>259 (64.11)</td>
<td>12 (2.97)</td>
<td>*</td>
<td>30 (7.43)</td>
</tr>
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<td>Acetazolamide</td>
<td>44 (26.04)</td>
<td>111 (65.68)</td>
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<td>*</td>
<td>*</td>
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<td><strong>Adrenergic Inhibitors</strong></td>
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<tr>
<td>Central Alpha-Antagonists</td>
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<td>347 (4.72)</td>
<td>105 (1.43)</td>
<td>241 (3.28)</td>
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<tr>
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<td>Calcium Channel Antagonists</td>
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<tr>
<td>Angiotensin II Receptor Blockers</td>
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<td>1619 (40.69)</td>
<td>451 (11.33)</td>
<td>123 (3.09)</td>
<td>303 (7.61)</td>
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<td>950</td>
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*Cannot be displayed due to restrictions regarding the publication of small cells in the data use agreement.*
Table S2. Among patients taking antihypertensives prior to pregnancy, patterns of antihypertensive dispensing during the second trimester. The Medicaid Analytic Extract Pregnancy Cohort.

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<tr>
<th>Antihypertensive type</th>
<th>Continue same antihypertensive</th>
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<th>Change to methyldopa</th>
<th>Change to labetalol</th>
<th>Change to other antihypertensive</th>
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<td>686 (16.2)</td>
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<td>339 (83.91)</td>
<td>15 (3.71)</td>
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<td>Calcium Antagonists And ACE Inhibitors</td>
<td>136 (29.44)</td>
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<tr>
<td>Other Combinations</td>
<td>39 (8.44)</td>
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<tr>
<td>Calcium Antagonists And ACE Inhibitors</td>
<td>37 (8.01)</td>
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<td>Other Combinations</td>
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<td>1206 (68.6)</td>
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<td>270 (15.36)</td>
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<td>Other Combinations</td>
<td>65 (3.7)</td>
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<tr>
<td>Calcium Antagonists And ACE Inhibitors</td>
<td>97 (5.52)</td>
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</table>

*Cannot be displayed due to restrictions regarding the publication of small cells in the data use agreement.*