Maternal and neonatal outcomes of antihypertensive treatment in pregnancy: a retrospective cohort study

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Abstract

Objective: To compare maternal and infant outcomes with different antihypertensive medications in pregnancy Design: Retrospective cohort study Setting: Kaiser Permanente, a large US healthcare system. Population: Women aged 15-49 years with a singleton birth from 2005-2014 treated for hypertension. Methods: We identified medication exposure from automated pharmacy data based on the earliest dispensing after the first prenatal visit. Using logistic regression, we calculated weighted outcome prevalences, adjusted odds ratios (aORs) and 95% confidence intervals, with inverse probability of treatment weighting to address confounding. Main outcome measures: Small for gestational age (SGA), preterm delivery, neonatal and maternal intensive care unit (ICU) admission, preeclampsia, and stillbirth or termination at >20 weeks. Results: Among 6346 deliveries, 87% with chronic hypertension, the risk of SGA (birthweight $<$ 10th percentile) was lower with methyldopa than labetalol (prevalence 13.6% vs. 16.6%; aOR 0.77, 95% CI 0.63 to 0.92). For birthweight $<$ 3rd percentile the aOR was 0.57 (0.39 to 0.80). Compared with labetalol (26.0%), risk of preterm delivery was similar for methyldopa (26.5%; aOR 1.10 [0.95 to 1.27]) and slightly higher for nifedipine (28.5%; aOR 1.25 [1.06 to 1.46]) and other β-blockers (31.2%; aOR 1.58 [1.07 to 2.23]). NICU admission was more common with nifedipine than labetalol (25.9% vs. 23.3%, aOR 1.21 [1.02 to 1.43]) but not elevated with methyldopa. Risks of other outcomes did not differ by medication. Conclusions: Risk of most outcomes was similar comparing labetalol, methyldopa and nifedipine. SGA risk was substantially lower for methyldopa, suggesting this medication may warrant further consideration.

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Short Title: Antihypertensive treatment in pregnancy

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Abstract

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Methods: We identified medication **e** xposure from automated pharmacy data based on the earliest dispensing after the first prenatal visit. Using logistic regression, we calculated weighted outcome prevalences, adjusted odds ratios (aORs) and 95% confidence intervals, with inverse probability of treatment weighting to address confounding.

Main outcome measures: Small for gestational age (SGA), preterm delivery, neonatal and maternal intensive care unit (ICU) admission, preeclampsia, and stillbirth or termination at > 20 weeks.

Results: Among 6346 deliveries, 87% with chronic hypertension, the risk of SGA (birthweight < 10th percentile) was lower with methyldopa than labetalol (prevalence 13.6% vs. 16.6%; aOR 0.77, 95% CI 0.63 to 0.92). For birthweight < 3rdpercentile the aOR was 0.57 (0.39 to 0.80). Compared with labetalol (26.0%), risk of preterm delivery was similar for methyldopa (26.5%; aOR 1.10 [0.95 to 1.27]) and slightly higher for nifedipine (28.5%; aOR 1.25 [1.06 to 1.46]) and other β-blockers (31.2%; aOR 1.58 [1.07 to 2.23]). NICU admission was more common with nifedipine than labetalol (25.9% vs. 23.3%, aOR 1.21 [1.02 to 1.43]) but not elevated with methyldopa. Risks of other outcomes did not differ by medication.

Conclusions: Risk of most outcomes was similar comparing labetalol, methyldopa and nifedipine. SGA risk was substantially lower for methyldopa, suggesting this medication may warrant further consideration.

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Keywords: antihypertensives, chronic hypertension, comparative effectiveness, hypertension, labetalol, methyldopa, nifedipine, pre-eclampsia, pregnancy, preterm delivery, real-world evidence, small for gestational age

"Tweetable" Abstract: Pregnant women with hypertension who took methyldopa were less likely to have infants born too small.

Introduction

Hypertensive disorders affect 5-10% of pregnancies,[1]increasing the risk of fetal growth restriction, stillbirth and other adverse outcomes.[2-5] About 160,000 pregnant women take antihypertensive medications annually in the US,[2] yet it is unclear which medication results in the best outcomes for women and infants. Current US and UK guidelines favor labetalol and nifedipine over methyldopa, while acknowledging uncertainty.[6,7] The International Society for the Study of Hypertension in Pregnancy has stated that both methyldopa and nifedipine are acceptable.[8]

Randomized clinical trials (RCTs) have not provided definitive evidence because they have had small sample sizes and heterogeneous methods. A 2018 Cochrane meta-analysis[9] found no evidence that any antihypertensive medication was superior to others in pregnancy, except that β-blockers and calcium channel blockers appeared more effective than methyldopa at preventing severe hypertension.[9] A recent RCT reported that methyldopa was associated with significantly lower risk of small for gestational age (SGA) and NICU admission compared to labetalol, with ORs on the order of 0.40, and that the two medications were associated with similar risk of severe maternal hypertension or preeclampsia.[10] The Control of Hypertension in Pregnancy Study, which randomized pregnant women to tight vs. less tight blood pressure control rather than to specific medications,[11] observed better pregnancy outcomes with methyldopa than labetalol,[12] but other antihypertensive medications were not examined. Many observational studies have compared women treated with an antihypertensive medication to unexposed women from the general pregnant population,[3,5,13-16] making it difficult to distinguish the risks of treatment from those of hypertension itself.

Because additional evidence is needed, we sought to compare the risk of important maternal and infant outcomes with use of different antihypertensive medications using electronic health records (EHR) data for a large, diverse US population.

Methods

Study population . This retrospective cohort study was conducted at Kaiser Permanente, a US healthcare system providing healthcare and insurance coverage. Participating regions were Washington, Southern California, and Northern California, which together serve about 8 million people generally representative of the surrounding communities.[17] Data came from EHRs and linked birth certificate data. These data have been used in many pregnancy studies,[18-21] and important variables and methods have been validated.[22-25] Study procedures were approved by the regions' institutional review boards and those of Washington State and California, with a waiver of consent.

The population was women age 15-49 years with a singleton live or stillbirth from 2005 through 2014. Women were required to be enrolled in Kaiser Permanente from 16 weeks' gestation through delivery, to have at least one blood pressure (BP) measured before 20 weeks, and to have chronic or gestational hypertension (defined from BP values, diagnosis codes and medication fills; our algorithm is shown in Table S1 and has been published[26]). We included both chronic or gestational hypertension because in clinical practice, it can be difficult to determine which type of hypertension is present and because these conditions may represent different points on a continuum of disease.

Women had to have filled at least one antihypertensive medication before 36 weeks gestation, to be on monotherapy, and to have been enrolled in Kaiser Permanente for at least 150 days before their qualifying fill. They could contribute more than one pregnancy to these analyses. We excluded deliveries exposed to teratogenic medications or certain high-risk maternal medical conditions (see Table S1 for more information). The sample size was determined by the number of eligible births.

Exposures. From pharmacy data, we identified fills for labetalol, methyldopa, nifedipine and other β-blockers (Table S1). We considered labetalol separately from other β-blockers because it is a combined α and β-blocker and unlike other β-blockers, it is recommended as first-line in US guidelines.[6] Exposure was defined based on the earliest fill after the first prenatal visit (typically at 8-10 weeks' gestation) or, if the visit date was unknown, at [?] 10 weeks gestation; we called this the 'index fill'. Using intent to treat principles, women's

exposure status was fixed rather than time-varying, because subsequent medication switches could be affected by the initial medication choice.

Outcomes. Outcomes included small for gestational age (SGA), preterm delivery, neonatal intensive care unit (NICU) admission, preeclampsia, maternal ICU admission, and stillbirth or termination at > 20 weeks. SGA was defined using sex and race-specific US birthweight curves.[27] The primary outcome was birthweight $<10^{\text{th}}$ percentile for gestational age and a secondary outcome $< 3^{\text{rd}}$percentile. Deliveries missing birthweight (n=32) were excluded from SGA analyses. We defined preterm delivery using gestational age from the EHR (preferentially) or birth certificate data, with the primary outcome being delivery before 37 weeks gestation and a secondary outcome, delivery before 34 weeks. We considered preterm delivery a potential measure of medication effectiveness, because less effective medications could lead to higher risk of uncontrolled maternal hypertension or fetal growth restriction (a potential consequence of severe hypertension) and via these pathways, to indicated preterm delivery. The automated data available to us do not reliably distinguish spontaneous vs. indicated preterm births. We identified ICU admissions using EHR data. Preeclampsia was identified from inpatient diagnosis codes after 20 weeks' gestation, an approach with a positive predictive value (PPV) of 90%.[28] We reviewed 45 charts meeting those criteria and found a PPV of 93%. We identified preeclampsia cases with "severe features" using modified criteria from the American College of Obstetricians & Gynecologists,[29] drawing on BP values, laboratory results and diagnosis codes (Table S1).

Potential stillbirths and terminations after 20 weeks' gestation were identified using EHR data; we included as outcomes the 76% of potential cases validated through medical record review or linkage to fetal death certificates. We grouped together stillbirths and terminations for several reasons. Terminations after 20 weeks might be done for fetal anomalies, which could in theory be affected by medication choice, as there is no definitive evidence about birth defect risk for some widely used antihypertensive medications. Also, the decision to terminate might be influenced by severe uncontrolled maternal hypertension, which could be a consequence of the initial medication choice. Finally, we hypothesized that variation in coding might lead to similar clinical scenarios being classified as either a stillbirth or termination in different instances.

Covariates . Covariates included maternal age at delivery, Kaiser Permanente region, delivery year, hypertension type (chronic or gestational), BP values, race/ethnicity, parity, maternal education, pregestational diabetes, depression, tobacco use, body mass index (BMI), and prior use of certain medications (Table S1). Hypertension was categorized as chronic if it was present prior to pregnancy or during the first 20 weeks gestation and as gestational otherwise. To account for hypertension severity, we identified the most recent BP value prior to the index fill and also determined whether a woman experienced one or more BPs [?] 160/110 before pregnancy or during this pregnancy before the index fill. We categorized history of antihypertensive medication use as no use prior to the index fill, continuous use up to the index fill (allowing for 80% adherence), or prior use with a gap. Other covariates included prior use of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, thiazide diuretics, diabetes medications, benzodiazepines, statins, antidepressants or antiseizure medications.

Analyses . Descriptive analyses included counts and proportions for categorical variables and means and standard deviations for continuous variables. Primary analyses used logistic regression to model study outcomes, with labetalol as the referent group. Inverse probability of treatment weights (IPTW) were used to account for confounding. We calculated weighted outcome prevalences for each medication group and adjusted odds ratios (aORs) and 95% confidence intervals (CIs). We used the bootstrap to account for multiple pregnancies per woman and for the estimation of the weights.[30,31] Treatment weights were generated from propensity scores calculated using a multinomial logistic regression model including all covariates shown in Table 1 except for BMI, education, parity, and timing of prenatal care. We omitted these variables because they were well balanced before weighting and a small proportion of deliveries had missing information for each of these characteristics. Table S2 lists variables in the propensity score. To improve statistical efficiency, we calculated stabilized weights including some baseline covariates in both the outcome model and the numerator of the weights.[32,33]These were Kaiser Permanente region, race/ethnicity, diabetes, type of hypertension (chronic vs. gestational), and gestational age at index fill.

For statistical modeling, we categorized delivery year as 2005-2008, 2009-2010, 2011-2012, and 2013-2014. We grouped together the four earliest years because very few deliveries were included from 2005-2006, when only one region had electronic BP values available. Maternal age was categorized as < 30, 30-34, 35-39 or [?] 40 years. Gestational age at the index fill was modeled as a linear spline with knots at 140 and 210 days. The systolic and diastolic BP values closest to the index fill were modeled using linear splines, with knots at 140 mm Hg and 90 mm Hg respectively. Deliveries missing race/ethnicity (0.5%) were grouped with those with "other" race/ethnicity and treated as a category of race/ethnicity in statistical models.

To assess covariate balance, we calculated the average standardized mean differences across all treatment groups before and after IPTW.[34,35]

We excluded stillbirths/terminations from analyses of SGA, NICU and preterm delivery because they are competing events. We used inverse probability of censoring weights to account for possible bias due to excluding stillbirths; Table S3 lists the variables used to model these weights.

In sensitivity analyses, we restricted the analysis to women with chronic hypertension (87% of the population) and excluded women with pregestational diabetes. In subgroup analyses, we examined new users separately from women with prior antihypertensive treatment. Analyses were performed using R, version 3.5.

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Patient involvement. There was no patient or public involvement in the study.

Results

Among 6346 eligible deliveries, there were 3017 (48%) where the woman had taken labetalol, 1834 (29%) methyldopa, 1105 (17%) nifedipine, and 390 (6%) other β-blockers. Figure 1 shows the impact of inclusion and exclusion criteria on the study population.

Mean maternal age was 33.6 years, 87% had chronic hypertension, and the mean gestational age at the index fill was 18.4 weeks. Many women (37%) were taking antihypertensive medication continuously prior to the index fill, and mean BPs prior to the index fill suggest that their hypertension was on average fairly well controlled. Table 1 shows baseline characteristics by treatment group, and Table S4 provides more detailed information for an expanded list of baseline characteristics. Table S5 shows characteristics by treatment group after IPTW and demonstrates that overall, these were well balanced (standardized mean difference < 0.1), except for those characteristics included in the outcome model, which are not expected to be balanced by IPTW. After IPTW, the group exposed to other β-blockers looked modestly different from the other groups, likely due to this group's small size. Table S6 and Figure S1 describe the distributions of propensity scores and weights.

Most women did not switch medications after their index fill. The proportion of women who later filled a different medication was 15% overall, ranging from 11 to 22% for different exposure groups.

Table 2 provides crude counts of outcomes by treatment group. Figure 2 shows the risk of maternal and neonatal outcomes comparing different medications, with labetalol as the referent group. We present weighted prevalences for outcomes after accounting for confounders together with adjusted ORs and 95% CIs. For SGA < 10^{th}percentile, risk was lower with methyldopa than labetalol (weighted prevalence 13.6% vs. 16.6%; aOR 0.77, 95% CI 0.63 to 0.92), and the association was stronger for birthweight < 3^{rd} percentile (aOR 0.57, 95% CI 0.39 to 0.80). The mean birthweight after IPTW was 3002 ± 797 g for labetalol, 3060 ± 788 g for methyldopa, 3033 ± 798 g for nifedipine, and 2944 ± 791 g for other β-blockers.

Preterm delivery was slightly more common with nifedipine than labetalol (28.5% vs. 26.0%; aOR 1.25, 95% CI 1.06 to 1.46), as was NICU admission (25.9% vs. 23.3%; aOR 1.21, 95% CI 1.02 to 1.43). β-blockers other than labetalol were associated with higher risk of preterm delivery (aOR 1.58, 95% CI 1.07 to 2.23).

Methyldopa and labetalol conveyed similar risks of preterm delivery and NICU admission. After IPTW, the mean gestational age at delivery was 37.6 ± 2.8 weeks for labetalol, 37.6 ± 2.8 weeks for methyldopa, 37.4 ± 2.8 weeks for nifedipine, and 37.4 ± 2.8 weeks for other β-blockers.

There was no significant association between medication type and risk of preeclampsia (overall or with severe features), maternal ICU admission, or stillbirth/termination.

Results of sensitivity and subgroup analyses are shown in Supplementary Figures S2-S4. Results did not change when we restricted the population to women with chronic hypertension, who made up 87% of the population. Results also did not change when we excluded women with pregestational diabetes. Some findings appeared qualitatively different when we limited analyses to new users; in this group, there was a suggestion of lower risk for many outcomes with methyldopa than with labetalol, with aORs around 0.5 to 0.7 (though most were not statistically significant).

Discussion

Main Findings

In this retrospective cohort study, the prevalence of many maternal and neonatal outcomes was similar with use of different antihypertensive medications. Compared to labetalol, the risk of SGA was significantly lower with methyldopa.

Strengths and Limitations

The large population improves precision and allows analyses not conducted in most prior studies, including examining labetalol separately from other β-blockers and directly comparing antihypertensive medications. We studied a diverse population in community practice and adjusted for many covariates including BP. Limitations include the potential for residual confounding because treatment was not randomized. Because we studied medication use in real world clinical practice, there were not uniform criteria for initiating or intensifying antihypertensive medications. It is possible that women filled medications but did not take them, leading to misclassification of exposure status. All women had health insurance and access to care and in general, their hypertension was well controlled at the time of the index fill, which may affect generalizability. Our data did not allow us to distinguish between spontaneous and indicated preterm birth, which on average would be expected to bias findings toward the null. The subgroup of women with gestational hypertension was too small to analyze separately. We did not have information about use of low dose aspirin, which the US Preventive Services Task Force recommended for women with chronic hypertension in 2014.[36] The mean difference in birthweight between medications was small, and it could be argued that a difference this small is not clinically important. While this may be true for infants in the normal range, even a small shift of the birthweight curve to the left could result in a large relative increase in infants born SGA or with low birth weight, which may have important consequences for the long term health of these infants.

Interpretation, in Light of Other Evidence

Most prior studies were small, yielding inconclusive results, and many observational studies compared treated women to healthy pregnant women, making confounding likely. Our finding of lower SGA risk with methyldopa compared to labetalol (aOR 0.77, 95% CI 0.63 to 0.92) is consistent with one recent RCT, which found the prevalence of SGA to be 21% with methyldopa vs. 41% with labetalol (OR 0.37, 95% CI 0.23-0.61).[10] Similar results were found by Magee et al. in a secondary analysis of RCT data.[12] The Cochrane meta-analysis of RCTs compared methyldopa to all β-blockers grouped together and reported a combined RR of 1.19 (0.76, 1.84). Grouping labetalol together with other β-blockers is problematic because it has different receptor specificity and thus may have different effects on outcomes. Another limitation is that the Cochrane analysis combined results from studies with heterogeneous methods.

We found a slightly higher risk of preterm delivery with nifedipine compared to labetalol in an analysis including over 4000 women. The Cochrane review found only one relevant RCT, a study of 112 women yielding an RR of 1.61 that was not statistically significant.[37] Our point estimate is compatible with theirs,

with greater precision. For NICU admission, we observed slightly higher risk with nifedipine than labetalol (aOR 1.21, 95% CI 1.02 to 1.43). Similarly, in a recent RCT of women with severe hypertension in pregnancy, NICU admission was more frequent with nifedipine (18%) than labetalol (10%), yielding a risk difference of 7.8 (95% CI 2.2 to 13.4).[38] The Cochrane meta-analysis reported a summary RR of 1.14 and 95% CI of 0.63 to 2.05, wide enough to be consistent with our finding. Still, since our study was not randomized, our findings could reflect confounding, including by indication for use, since nifedipine is also used for tocolysis. Many women who took nifedipine did so fairly early in pregnancy; the median gestational age at index fill for nifedipine was 20.8 weeks (compared to 18.8 weeks for labetalol), which provides evidence that much of the use we observed was in fact for hypertension.

Current US guidelines recommend labetalol and nifedipine above other medications and state that methyldopa is less preferred because of possible lower effectiveness and adverse effects.[39] UK guidelines recommend labetalol, followed by nifedipine and then methyldopa.[7] There is little evidence to support these recommendations, and several older RCTs suggested that labetalol and methyldopa are equally effective in lowering BP.[40-42]If methyldopa were less effective in controlling maternal BP, this might increase the risk of other harmful outcomes such as preeclampsia or indicated preterm birth, a pattern that we did not observe. While recognizing the potential for unmeasured confounding, our large observational study suggests that outcomes are very similar between methyldopa and labetalol, except for SGA. We suggest that for hypertensive pregnancies where there is substantial concern for SGA, it may be reasonable to give more consideration to methyldopa.

While it is concerning that labetalol appeared to convey higher risk of SGA, infants born SGA have variable trajectories: they may remain small, return to a normal growth curve or experience compensatory weight gain leading to childhood obesity. Future studies should examine child growth and development.

Conclusions

In this large retrospective study, the prevalence of most maternal and infant outcomes was similar with different antihypertensive medications. A significantly lower risk of SGA was seen for methyldopa than labetalol, which is noteworthy because methyldopa is not preferred in US or UK guidelines.[6,7]Our results suggest that methyldopa may warrant additional consideration, especially in pregnancies for which there is heightened concern about growth restriction.

Disclosure of Interest:LC is now employed by Genentech. ZBC is now employed by Roche Pharmaceuticals. TRE has consulted for Alnylam Pharmaceuticals, DiabetOmics, and Ferring Pharmaceuticals. SMS has received grant funding through her institutions from Syneos Health, LAA received funding through her institution from Bausch Health Companies, KR from Novartis and Merck & Co., and SD from GSK. Other authors report no conflict of interest.

Contributions to Authorship: SD, LAA, TCC, TRE, LC, VLH, RSN, SEB, and SMS contributed to the conception and design of the study. SD, TCC and LAA obtained funding. NN and ZBC extracted study data. MA performed statistical analyses with guidance from SMS. SD, SMS, TCC, LAA and KR provided supervision. All authors participated in interpretation of results; SD, MA and SMS drafted the manuscript; and all authors participated in revision of the manuscript. All authors accept responsibility for the paper as submitted.

Details of Ethics Approval: Study procedures were approved by the regions' institutional review boards and those of Washington State and California, with a waiver of consent. The study received initial approval from the Kaiser Permanente Washington Institutional Review Board on October 8, 2015 under file number 806302; from the KP Southern California Institutional Review Board on January 12, 2016 (file number 10913), and from the KP Northern California Institutional Review Board on 8/24/2015under file number CN-15-2337-H/1277850. At KP Northern California, it was subsequently considered exempt beginning in 2019 due to changes to the US Common Rule. This work was also approved by the Washington State Institutional Review Board on July 21, 2015, under file number D-082213-H14.01 and by the California State Institutional Review Board on 1/19/2016 under file number 15-07-2118.

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List of Table and Figure Captions

Table 1. Baseline characteristics of the population before weighting, by treatment group

Table 2. Counts of maternal and neonatal outcomes by treatment group

Figure 1. Impact of inclusion and exclusion criteria on study population.*

*A woman may meet more than one exclusion criterion within a box. Detailed information about inclusion and exclusion criteria is found in Table S1.

+The index fill was defined as the earliest fill after the first prenatal visit (typically at 8-10 weeks' gestation) or, if the visit date was not known, at [?] 10 weeks gestation.

Abbreviations: BP, blood pressure; KPNC, Kaiser Permanente Northern California; KPSC, Kaiser Permanente Southern California; KPWA, Kaiser Permanente Washington.

Figure 2. Risk of maternal and neonatal outcomes with use of different antihypertensive medications in pregnancy.*

*ORs and 95% CIs are calculated after inverse probability of treatment weighting. Labetalol is the referent group. The population for different outcomes differs slightly because pregnancy losses were not included in the denominator for SGA, preterm delivery, or neonatal ICU admission. For most outcomes, the total N is 6346, for SGA the total N is 6240, and for preterm delivery and NICU admission the total N is 6272.

**Weighted prevalence in the subgroup, calculated using inverse probability of treatment weighting with unstabilized weights.

Abbreviations: OR, odds ratio; CI, confidence interval; SGA, small for gestational age; ICU, intensive care unit.

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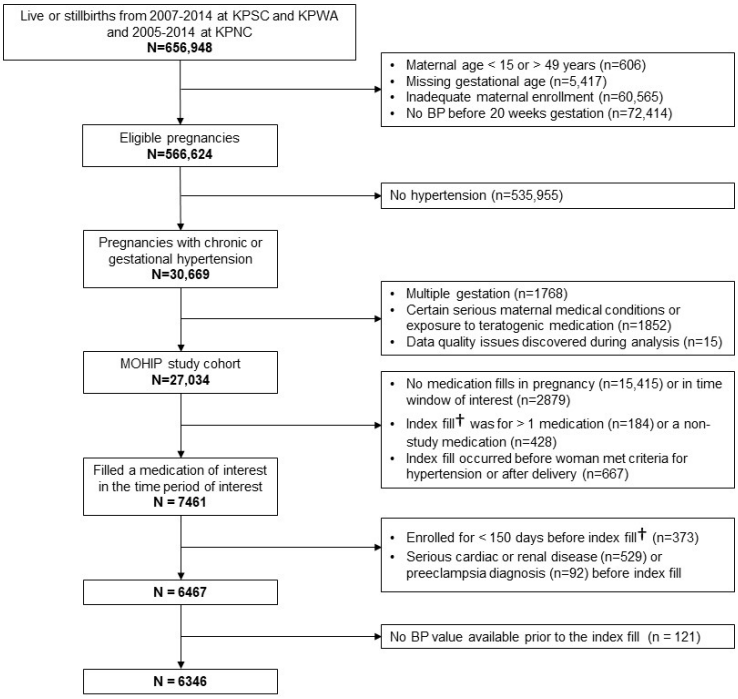

*A woman may meet more than one exclusion criterion within a box. Details about inclusion and exclusion criteria are in Supplemental Appendix Table 1.
†The index fill was defined as the earliest fill after the first prenatal visit (typically at 8-10 weeks' gestation) or, if the visit date was not known, at ≥ 10 weeks gestation.

Abbreviations: BP, blood pressure; KPNC, Kaiser Permanente Northern California; KPSC, Kaiser Permanente Southern California; KPWA, Kaiser Permanente Washington.