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Master Thesis

Oral antihypertensive agents in pregnancy and fetal growth restriction – a population-based cohort study

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Abstract

Introduction Currently, there is no consensus on whether methyldopa, labetalol, or nifedipine is the preferred treatment for hypertension in pregnancy. These agents might have varying effects on fetal growth and the risk for small for gestational age (SGA) birth. Randomised controlled trials lack sufficient power to determine if one of the three agents poses an increased risk regarding this outcome.

Methods In this population-based cohort study, automated pharmacy dispensing data (PHARMO) was linked to the Netherlands Perinatal Registry (Perined) for outcomes of pregnancies between 2000-2019. Using multivariate logistic regression analysis, we retrospectively assessed the effect of methyldopa, labetalol and nifedipine on the outcome SGA.

Results The risk of SGA birth was not significantly different for pregnancies exposed to labetalol compared to methyldopa (adjusted odds ratio (aOR) = 0.94, 95% confidence interval (CI): 0.81-1.10, p=0.47). Due to the inclusion of pregnancies where nifedipine was used as a tocolytic agent for threatened preterm delivery, this treatment could only be validly compared with the other two agents in the chronic hypertension subgroup analysis (start of treatment < 20 weeks gestational age). In this subgroup, the risk of SGA birth for nifedipine was comparable to that of methyldopa (aOR=1.11, 95% CI: 0.71–1.68, p=0.22) and labetalol (aOR=1.01, 95% CI: 0.63–1.59, p=0.93).

Conclusion Our findings suggest that there is no difference in the risk of SGA birth between methyldopa, labetalol and nifedipine. Large-scale observational studies using other data sources with more elaborate data on covariates and treatment indication are needed for confirmation.

Introduction

Hypertensive disorders of pregnancy are a leading cause of morbidity and mortality for mother and child worldwide, complicating up to 10% of all pregnancies.[1-3] As such, a substantial proportion of antenatal care is devoted to their detection and treatment.[4] Affected women are at increased risk for developing adverse events, including severe hypertension or hypertensive crisis; haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome; eclampsia; stroke; pulmonary oedema and death.[2,4,5] The fetus, due to uteroplacental dysfunction associated with pregnancy hypertension, is susceptible to fetal growth restriction (FGR) and being born small for gestational age (SGA). Furthermore, when the severity of the maternal clinical condition necessitates pregnancy termination before term gestational age, iatrogenic preterm birth may result in neonatal complications.[3,6-8]

Strict blood pressure control in women with mild to moderate hypertension has been shown to effectively ameliorate the risk of developing severe hypertension and improve pregnancy outcomes.[9,10] Hence, oral antihypertensive agents are routinely administered to this group, aiming to facilitate a safe term pregnancy without adverse effects for both mother and child. However, past studies have described a potential association between individual antihypertensive drugs and FGR, in a group that is already at risk for this outcome.[6,11-16] The different types of oral antihypertensive agents could affect uteroplacental blood flow due to systemic blood pressure decrease or have direct pharmacological effects on placental and/or maternal vascular function.[17] Since low birth weight is linked to an increased risk of perinatal morbidity, mortality and neurodevelopmental abnormalities,[18] clarifying the impact of different antihypertensives on fetal growth is crucial.

Currently, three oral antihypertensive agents are primarily used in obstetrics: methyldopa, an α2-receptor agonist; labetalol, an α- and β-adrenergic antagonist; and nifedipine, a calcium-channel blocker.[2] The present national and international guidelines lack consensus on the preferred option among these three agents.[1,2,19-22] Therefore, obstetric professionals are obliged to make their choice of agent mostly based on expert opinion. While methyldopa is the most frequently used and widely regarded as the safest option, it has notable maternal side effects (e.g. drowsiness, nausea, depression and hallucinations).[2,23,24] Moreover, labetalol and nifedipine have been demonstrated to be superior in preventing severe hypertension.[25] Yet, these two agents are not consistently regarded as preferred treatment options. This may be attributed to the association between beta-blockers, such as labetalol, and SGA birth reported in several observational studies[12-15] and the limited availability of evidence regarding safety outcomes for nifedipine.[4,25]

Consequently, labetalol and nifedipine are currently not officially approved as 'safe during pregnancy' in the Netherlands.

Recently performed meta-analyses of randomised controlled trials (RCT) did not confirm a potential relationship between SGA and any of the three agents.[4,25] However, most included trials comparing drugs head-to-head are limited in sample size and therefore lack statistical power, precluding definitive conclusions. A trial sequential analysis conducted by Bone et al. (2022) demonstrated that to adequately compare the three agents, approximately 10,000 patients are required.[4] As setting up an RCT of such a scale is infeasible and financially unviable, it is likely that we will continue to lack sufficient trial evidence to fully inform clinical decision-making.

Therefore, we propose an alternative research method in this study. Using linked population-based data from national registries on pregnancy outcomes and pharmacy dispensing in the Netherlands, we retrospectively assessed the effect of methyldopa, labetalol and nifedipine on the risk of SGA birth. The primary objective was to determine if one of the three agents poses an increased risk regarding this outcome.

Methods

Data sources

We conducted this retrospective cohort study in women who received methyldopa, labetalol or nifedipine during pregnancy using the PHARMO Perinatal Research Network (PPRN) as our data source. The PPRN links the Netherlands Perinatal Registry (Perined) and the PHARMO Database Network. Perined is a nationwide linked database combining medical registries from general practitioners, midwives, gynaecologists and neonatologists/ paediatricians. Virtually all pregnancies (~99%) in the Netherlands with a gestational age of at least 16 weeks are encompassed in this registry, providing data on both maternal and neonatal characteristics. PHARMO is a population-based network of healthcare databases, combining data from electronic medical records of inpatient and outpatient pharmacies, general practices and hospitals. All patients from participating healthcare providers are included, except those who specifically opted out. The established database provides detailed information on all medication prescriptions and dispensings of the included patients. The linkage between PHARMO and Perined is primarily based on the birth dates of mother and child, gender and postal codes. A linkage with PHARMO was feasible for about 20% of the pregnancies in Perined. The characteristics of the PPRN cohort and the linkage process have been described in more detail in the cohort profile article by Houben et al.[26]

Study population

We selected all pregnancies with (1) a feasible linkage between PHARMO and Perined and with (2) at least one dispensing of methyldopa, labetalol, or nifedipine between 2000 and 2019. The cutoff year of 2019 was intentionally chosen to exclude the period of the COVID-19 pandemic due to its significant impact on obstetric care. Pregnancies were excluded when (1) birth weight was below 500 grams, (2) gestational duration was unknown, (3) gestational duration was shorter than 23 weeks or longer than 42 weeks, (4) congenital abnormalities were present, or (5) the sex of the neonate was unknown.

Exposures

We postulated that a minimum use of one week is required for an antihypertensive agent to potentially exert any influence on birth weight. Therefore, we determined exposure to the antihypertensive agents for each pregnancy by accumulating all dispensed doses per agent, excluding those from the final week of gestation. If this cumulative dose for any of the agents exceeded the minimum dosage for one week, we considered the pregnant woman exposed to that specific agent. The values adopted as the minimum dosages for a week were 3500 milligrams (mg) for methyldopa, 1050 mg for labetalol, and 140 mg for nifedipine, in accordance with the Dutch guideline.[27] In the head-to-head comparison of the three drugs, pregnant women exposed to more than one agent were excluded. Yet, these women were used in the comparison between polytherapy and monotherapy.

Outcomes

The primary outcomes of interest were SGA, defined as a birth weight <10th percentile for gestational age, and birth weight < 3rd percentile. The percentiles were determined using the Dutch Hoftiezer birth weight charts published in 2019.[28] Secondary outcomes of interest were low birth weight (LBW), defined as a birth weight < 2500 grams, birth weight as a continuous outcome, and z-scores of the birth weight. Z-scores were calculated using the reference population of the Hoftiezer birth weight charts and, like percentiles, were corrected for gestational age and sex.

Covariates

The following characteristics in the study population were regarded as covariates: maternal age at delivery, parity, socioeconomic status (SES), hypertension type (chronic hypertension (CH) and pregnancy-induced hypertension (PIH)) and preconceptional use of other antihypertensive agents (diuretics, calcium channel blockers and agents acting on RAAS). SES was determined based on the postal code of the mother. Hypertension type was based on the date of the first dispensing of an antihypertensive agent. If the dispensing occurred after 20 weeks of gestation, it was classified as PIH; otherwise, it was considered CH. Additionally, concurrent uses of certain medications, such as antidiabetic agents, immunosuppressants (e.g., corticosteroids and biologicals), beta-blocking agents other than labetalol, anticonvulsive agents, and antidepressants, were considered covariates.

Statistical analysis

The maternal and perinatal characteristics were summarized according to exposure group (methyldopa, labetalol, nifedipine or polytherapy) using frequencies and percentages for categorical variables and means (M) with standard deviations (SD) for continuous variables.

Multivariate logistic regression analysis was utilized to compute adjusted odds ratios (aOR) for the outcomes SGA and LBW, comparing the following treatment groups: methyldopa vs. labetalol; methyldopa vs. nifedipine; labetalol vs. nifedipine; and polytherapy vs. monotherapy. The odds ratios were adjusted for the aforementioned covariates. Subgroup analyses were performed for women with PIH and CH, with and without preeclampsia (PE) and with and without severe hypertension (sHT). Patients were deemed to have PE when the diagnosis was registered in Perined or when proteinuria was present. sHT was defined by the highest recorded diastolic pressure exceeding 110 mmHg

during pregnancy. To compare the mean birth weight and z-scores between treatment groups, one-way ANOVA was used.

All statistical analyses were performed using R (version 4.3.0) and RStudio.

Results

Study population

From the PPRN, 10,640 pregnancies were selected with at least one dispensing of methyldopa, labetalol or nifedipine between 2000 and 2019. After applying the exclusion criteria, 8,973 pregnancies remained for analysis. The individual impact of exclusion criteria is shown in *Figure 1*.

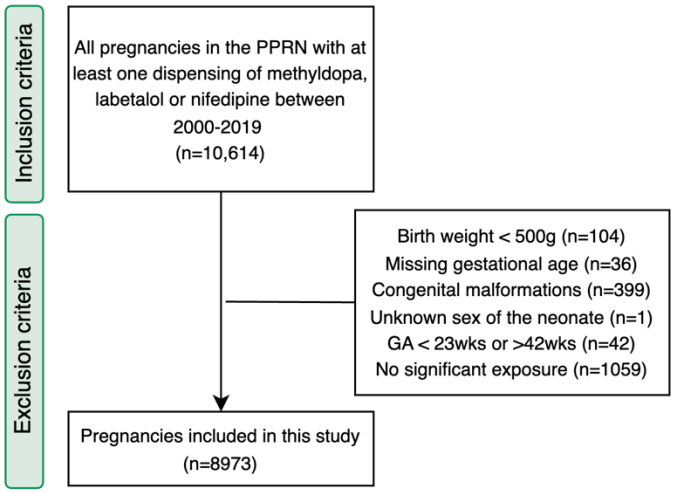

Fig. 1: Flow diagram of patient selection into the study cohort
PPRN: PHARMO Perinatal Research Network, GA: Gestational age, wks: weeks.

Nearly 90% of the pregnancies were exposed to a single agent, with the remainder categorised as polytherapy. Methyldopa was the most commonly used antihypertensive agent, followed by labetalol and nifedipine. The frequencies for each therapy per subgroup are shown in *Table 1*.

Table 1: Frequencies of exposure to antihypertensive agents and combinations

	All	PIH	CH	PE
Monotherapy	7986 (89.0)	4443 (94.3)	3543 (83.1)	1263 (84.4)
Methyldopa	5900 (65.8)	33387 (71.9)	2513 (59.0)	1073 (71.7)
Labetalol	1391 (15.5)	528 (11.2)	863 (20.3)	157 (10.5)
Nifedipine	695 (7.7)	528 (11.2)	167 (3.9)	33 (2.2)
Polytherapy	987 (11.0)	269 (5.7)	718 (16.9)	233 (15.6)
Total	8973 (100)	4712 (100)	4261 (100)	1496 (100)

Data are n (%), PIH: Pregnancy-induced hypertension, CH: Chronic hypertension, PE: Preeclampsia, M: Methyldopa, L: Labetalol, N: Nifedipine.

Table 2 details the characteristics of the pregnancies grouped by treatment, including polytherapy. Pregnancies exposed to methyldopa and labetalol were largely comparable; however, labetalol was more often prescribed to women with CH. The nifedipine-exposed pregnancies displayed differences from the other two single exposure groups. The mean maternal age was lower, preterm births occurred nearly twice as often and there were fewer inductions or caesarean sections. PE and sHT were also less frequent in this group. Mainly due to more frequent CH, use of antidiabetic agents, PE, and sHT, the polytherapy group was not comparable to the monotherapy groups.

Table 2: Characteristics of included pregnancies

	Methyldopa (n=5900)	Labetalol (n=1391)	Nifedipine (n=695)	Polytherapy (n=987)
Maternal characteristics				
Age (years; *M±SD)*	32.2 ± 4.7	32.6 ± 4.7	30.7 ± 5.4	33.4 ± 4.8
Nulliparous	2817 (47.7)	590 (42.4)	287 (41.3)	425 (43.0)
SES				
Low	1811 (30.7)	394 (28.3)	224 (32.2)	325 (32.9)
Middle	1996 (33.8)	507 (36.4)	245 (35.3)	331 (33.5)
High	2061 (34.9)	488 (35.1)	224 (32.2)	328 (33.2)
Comedication				
Antidiabetic agents[a]	281 (4.8)	78 (5.6)	37 (5.3)	80 (8.1)
Beta blockers	149 (2.5)	61 (4.4)	33 (4.7)	50 (5.1)
Immunosuppressants	96 (1.6)	47 (3.4)	17 (2.4)	16 (1.6)
Anticonvulsive agents	15 (0.3)	6 (0.4)	9 (1.3)	1 (0.1)
Antidepressants	202 (3.4)	56 (4.0)	31 (4.4)	40 (4.1)
Hypertension characteristics				
PIH	3378 (57.4)	528 (38.0)	528 (76.0)	269 (27.3)
CH	2513 (42.6)	863 (62.0)	167 (24.0)	718 (72.7)
Prior AH use[b]	847 (14.4)	308 (22.1)	69 (9.9)	262 (26.5)
Preeclampsia	1073 (18.2)	157 (11.3)	33 (4.7)	233 (23.6)
sHT	1063 (18.0)	184 (13.2)	19 (2.7)	276 (28.0)
Neonatal characteristics				
GA (wk+d; *M±SD)*	38+0 ± 17	38+3 ± 16	37+3 ± 18	37+0 ± 22
< 37 wks	1171 (19.8)	222 (16.0)	234 (33.7)	325 (32.9)
< 32 wks	200 (3.4)	38 (2.7)	24 (3.5)	76 (7.7)
Induced / C-section	3843 (65.1)	898 (64.6)	314 (45.2)	747 (75.7)
Male sex	3050 (51.7)	740 (53.2)	391 (56.3)	487 (49.3)

Data are n (%) unless stated otherwise, M: Mean, SD: Standard deviation, SES: Socio-economic status, PIH: Pregnancy-induced hypertension, CH: Chronic hypertension, sHT: Severe hypertension, AH: Antihypertensive, GA: Gestational age, wk: Week, d: day,
[a] Use of any antidiabetic agent preconceptionally or use of insulin during pregnancy.
[b] Preconceptional use of diuretics, other calcium channel blockers or agents acting on RAAS.

Small for gestational age

The risk for SGA birth (< 10th percentile) was not significantly different for pregnancies exposed to labetalol compared to methyldopa (aOR=0.94, 95% CI: 0.81-1.10, p=0.47). Use of nifedipine was correlated with a lower risk of SGA birth than methyldopa (aOR=0.74, 95% CI: 0.60-0.91, p<0.01). There was no significant difference when nifedipine was compared to labetalol (aOR=0.93, 95% CI: 0.72-1.22, p<0.63). The adjusted odds ratios were largely comparable for the outcome birth weight below 3rd percentile. (*Table 3)*

Subgroup analyses

Subgroup analyses for the outcome SGA are shown in *Table 3* for subgroups PIH, CH and PE, and in *Supplementary Table 1* for no PE, sHT and no sHT. Contrary to the entire group, there was a decreased risk of SGA birth for labetalol compared to methyldopa in the PIH (aOR=0.78, 95% CI: 0.62-0.98, p=0.04) and PE subgroups (aOR=0.62, 95% CI: 0.41-0.93, p=0.03). For the comparison between nifedipine and methyldopa, the odds ratio aligned with the entire group in the PIH subgroup (aOR=0.65, 95% CI: 0.51-0.83, p<0.01); however, no difference between the two agents was observed in the remaining subgroups. The subgroup analysis outcomes for nifedipine vs. labetalol were consistent with those of the entire group.

Birth weight and z-score

Neonates of whom mothers used labetalol during pregnancy had the highest birth weight (*M±SD* = 3134±695), followed by those exposed to methyldopa (*M±SD* = 3057±736). Nifedipine

Table 3: Oral antihypertensive agents in pregnancy and SGA birth

Labetalol vs. Methyldopa

	Labetalol	Methyldopa	Adjusted OR[a] (95% CI)	*p*
SGA < p10 - All	254/1389 (18)	1225/5867 (21)	0.94 (0.81 – 1.10)	0.47
PIH	105/527 (20)	837/3373 (25)	0.78 (0.62 – 0.98)	0.04
CH	149/862 (17)	388/2494 (16)	1.11 (0.90 – 1.37)	0.31
PE	37/157 (24)	377/1067 (35)	0.62 (0.41 – 0.93)	0.03
SGA < p3	104/1389 (7)	524/5867 (9)	0.92 (0.73 – 1.15)	0.47

Nifedipine vs. Methyldopa

	Nifedipine	Methyldopa	Adjusted OR[a] (95% CI)	*p*
SGA < p10 - All	115/693 (17)	1225/5867 (21)	0.74 (0.60-0.91)	<0.01
PIH	86/527 (16)	837/3373 (25)	0.65 (0.51 – 0.83)	<0.01
CH[b]	29/166 (17)	388/2494 (16)	1.11 (0.71 – 1.68)	0.22
PE	10/33 (30)	377/1067 (35)	0.81 (0.36 – 1.71)	0.59
SGA < p3	46/693 (7)	524/5867 (9)	0.71 (0.51 – 0.96)	0.03

Nifedipine vs. Labetalol

	Nifedipine	Labetalol	Adjusted OR[a] (95% CI)	*p*
SGA < p10 - All	115/693 (17)	254/1389 (18)	0.93 (0.72 – 1.22)	0.63
PIH	86/527 (16)	105/527 (20)	0.87 (0.62 – 1.22)	0.44
CH[b]	29/166 (17)	149/862 (17)	1.01 (0.63 – 1.59)	0.93
PE	10/33 (30)	37/157 (24)	1.26 (0.51 – 3.01)	0.59
SGA < p3	46/693 (7)	104/1389 (7)	0.93 (0.62 – 1.36)	0.69

Data are n/N (%), SGA: Small for gestational age, OR: Odds ratio, CI: Confidence interval, PIH: Pregnancy-induced hypertension, CH: Chronic hypertension, PE: Preeclampsia

[a] Adjusted for maternal age, parity, diabetes mellitus, socio-economic status, hypertension type, prior use of antihypertensives and comedication.

[b] Only in this group, pregnancies where nifedipine was used as a tocolytic agent were excluded

exposed offspring had the lowest average birth weight (*M±SD* = 2933±736). The mean z-scores did not significantly differ among the three medication groups (methyldopa (*M±SD*) = -0.26±1.41, labetalol = -0.21 ± 1.34, nifedipine = -0.27 ± 1.24, p=0.42) (*Table 4)*. Mean birth weights of subgroups are shown in *Supplementary Table 2.*

Table 4: Birth weight and Z-scores

	Methyldopa	Labetalol	Nifedipine	*p*
Birth weight	3057 ± 736	3134 ± 695	2933 ± 707	<0.01
Z-scores	-0.26 ± 1.41	-0.21 ± 1.34	-0.27 ± 1.24	0.42

Data are M±SD, M: Mean, SD: Standard deviation.

Low birth weight

The risk for LBW (<2500g) was higher for nifedipine when compared to methyldopa (aOR=1.58, 95% CI: 1.31-1.90, p<0.01) and labetalol (aOR=1.98, 95% CI: 1.55-2.52, p<0.01). Between methyldopa and labetalol, there was no distinction in the risk for LBW (aOR=0.88, 95% CI: 0.74-1.03, p=0.11). (*Supplementary Table 3*).

Polytherapy compared with monotherapy

Compared to monotherapy, exposure to polytherapy was associated with an increased risk for birth weight < 10th percentile (aOR=1.98, 95% CI: 1.69-2.30, p<0.01), Results were similar in all subgroup analyses. (*Supplementary Table 4*)

Discussion

In this large retrospective cohort study, we sought to compare the effects of the three primary oral antihypertensives during pregnancy—methyldopa, labetalol, and nifedipine—on SGA birth and birth weight using population-based data from national registries.

Summary and interpretation of findings

Our results indicate similar risks of SGA birth in the comparison of labetalol with both methyldopa and nifedipine. We did find a diminished risk for nifedipine when compared to methyldopa. However, the characteristics of pregnancies treated with nifedipine were markedly distinct from those treated with methyldopa, with less severe hypertension and more preterm birth. These group differences may be attributed to the fact that nifedipine is used as both an antihypertensive and a tocolytic agent for threatened preterm labour in several Dutch hospitals.[29] Incorporating these pregnancies without hypertension-related uteroplacental dysfunction into the nifedipine group may have caused a misrepresentation of the risk for SGA birth relative to methyldopa and labetalol. Nonetheless, nifedipine may be validly compared with the other two agents in the CH subgroup analysis. Since treatment was started before 20 weeks of gestation in this subgroup, pregnancies where nifedipine was used as a tocolytic were likely excluded. In the CH group, the risk of SGA for nifedipine was comparable with methyldopa and labetalol. This suggests that there is no difference in the risk of SGA birth among the three oral antihypertensives. Additionally, we found a reduced incidence of SGA with labetalol compared to methyldopa in the PIH and PE subgroups. This could be attributed to confounding by indication. Labetalol might be more frequently avoided in the Netherlands when there is a suspicion of FGR. Given that fetal growth is often assessed when a PIH or PE diagnosis is made, this could have influenced the results in these groups. In the CH subgroup, this likely has less impact. Besides comparing the three oral antihypertensive agents, we also evaluated polytherapy versus monotherapy. The characteristics of the polytherapy group indicated that this treatment is prescribed to those more severely affected by their hypertensive condition than the monotherapy group. Given these pronounced differences, it was not feasible to adequately compare the effect of polytherapy and monotherapy on SGA. In comparing average birth weights, significant differences emerged among the three medication groups. Pregnancies exposed to labetalol had the highest birth weight, followed by methyldopa, with nifedipine having the lowest. This is likely influenced by the use of nifedipine as a tocolytic agent and therefore high rates of preterm birth in this group. The variation in birth weight across groups may largely be attributed to differences in average gestational age. This is further supported by the non-significant differences between the three treatment groups in average z-scores, which are corrected for gestational age.

Comparison with current literature

The results of this study align with those of the recently performed network meta-analysis by Bone et al. (2022)[4], in which no distinction was observed between antihypertensives regarding SGA. Indeed, with the inclusion of more patients, the confidence intervals around our point estimates are considerably less wide, suggesting greater certainty in this result. This applies primarily to the comparison between labetalol and methyldopa.

Several observational studies have found an increased risk of SGA birth for beta-blockers, in contrast to our findings.[12,14,15] However, analysing beta-blockers as a group might obscure the effects of individual drugs, especially for labetalol, given its distinct receptor specificity (α and β-blocking properties). As such, aligning our results with these studies might not be appropriate. A recently published population-based cohort study by Dublin et al. (2022)[30] did analyse labetalol separately from other beta-blockers. The study used a methodology similar to ours, deriving antihypertensive exposure from computerized pharmacy data, which was linked with birth certificates for pregnancy outcomes. Nonetheless, a decreased risk for SGA birth was found in pregnancies exposed to methyldopa compared to labetalol, contradicting our results as well. Confounding by indication and different definitions for exposure may account for the dissimilar outcomes of our study and theirs. Firstly, the study by Dublin et al. was performed in the US where labetalol is preferred over methyldopa in the treatment of pregnancy hypertension[20], in contrast to the Netherlands. As a result, the study by Dublin may have had a distinct cohort of women exposed to labetalol compared to ours. Additionally, Dublin et al. excluded pregnancies with a first dispensing after 36 weeks. Excluding this less severely affected group could have altered the results, especially if one drug was predominantly prescribed within it. Finally, exposure groups were defined based on the intention-to-treat principle, meaning pregnancies were categorized by the initial medication dispensed, regardless of subsequent changes or additions. In our study, women who switched medication or received an additional drug were categorised as polytherapy, using the per-protocol principle. Consequently, Dublin et al. classified a subset of pregnancies under monotherapy that would have been categorised as polytherapy and excluded from direct drug comparisons in our study. In this group, hypertension was likely less controlled, indicating more pronounced placental insufficiency and elevated risk for SGA. Since labetalol is often the initial choice in the US, the proportion of these multi-exposure cases is presumably higher in this treatment group, resulting in an increased risk of SGA birth.

Strengths and limitations

This study has several strengths. Most importantly, it is currently the study with the largest sample size that compares oral antihypertensive agents in pregnancy head-to-head. We directly compared the three most used antihypertensive agents without grouping them together with other agents. Furthermore, unlike other studies, we set a minimum threshold for exposure where we anticipated a potential impact of the antihypertensives on birth weight.

Nevertheless, the results of our study should be interpreted in light of certain limitations. While our sample size was indeed substantial, the bulk was concentrated in the methyldopa group because of its favoured status in the Netherlands. The nifedipine group was notably smaller. Moreover, since the PPRN lacks information on treatment indication and diagnoses, it was not possible to exclude all pregnancies where nifedipine was used as tocolytic agent. Therefore, nifedipine could only be adequately compared with other agents within the even smaller subgroup with CH. This real-world data did not provide insight into treatment adherence. Of course, dispensing of medication does not necessarily indicate its consumption. However, de Jong et al.[31] reported that 94% of all medication dispensed to pregnant women are consumed. While we aimed to adjust for more key covariates like Body Mass Index, smoking, and ethnicity, inadequate registration in Perined rendered this infeasible. Other poorly recorded variables in Perined include PE and sHT, so these subgroup analyses should be interpreted with caution. Finally, an inherent limitation of the observational design of this study is the potential for unmeasured confounding.

Recommendations for future research

The optimal study design to adequately compare oral antihypertensive agents for pregnancy outcomes would be a large RCT. However, as previously mentioned, conducting such a large trial is practically unattainable. Future research should therefore concentrate on refining big data observational studies, akin to our approach. Other data sources should be explored for use in similar studies. Utilizing more accurate data sources, like electronic health records, would allow for adjustment of more confounding factors such as smoking, Body Mass Index, ethnicity, and additional comorbidities. Furthermore, data from electronic health records on diagnoses (ICD codes) enables the exclusion of pregnancies where nifedipine is used as a tocolytic agent for threatened preterm labour, thus eliminating this limitation. In addition, incorporating multiple data sources may increase the sample size, allowing for more robust methods to adjust for confounding, such as inverse probability weighting or propensity score matching. This could reduce the potential for residual confounding and possibly facilitate causal inference.

This study underlines that utilizing 'big data' is suitable for addressing clinical questions within obstetrics. Given the vulnerable population of pregnant women and unborn children, this field is particularly well-suited for this non-invasive research approach. When designing future studies, this should be taken into consideration.

Clinical implications

Clinicians and several guidelines currently hesitate to prefer labetalol or nifedipine over methyldopa due to concerns for adverse effects like FGR. The results of our study suggest no increased incidence of SGA with labetalol or nifedipine. Therefore, our recommendation for clinical practice would be to prioritize other factors in the choice for an antihypertensive agent in individual patients, like efficacy and side effects.

Conclusion

The results of this population-based cohort study reveal no difference in the risk of SGA birth when comparing methyldopa, labetalol, and nifedipine as treatment of hypertension in pregnancy. For methyldopa and labetalol, this assertion is more definitive than for nifedipine. Due to a smaller sample size and the inevitable inclusion of patients using nifedipine as a tocolytic agent, results for this group are less certain. Therefore, future research using other data sources with information on treatment indication is needed to confirm the findings of this study.

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Appendix

Supplementary table 1: Subgroup analysis SGA

Labetalol vs. Methyldopa

	Labetalol	Methyldopa	Adjusted OR[a] (95% CI)	*p*
SGA < p10 - no PE	217 / 1232	848 / 4800	1.09 (0.92 – 1.29)	0.33
sHT	47 / 184	354 / 1058	0.75 (0.52 – 1.08)	0.13
no sHT	169 / 1010	765 / 4285	1.04 (0.86 – 1.26)	0.64

Nifedipine vs. Methyldopa

	Nifedipine	Methyldopa	Adjusted OR[a] (95% CI)	*p*
SGA < p10 - no PE	105 / 660	848 / 4800	0.87 (0.69 – 1.09)	0.14
sHT	6 / 18	354 / 1058	1.10 (0.37 – 2.94)	0.85
no sHT	97 / 605	765 / 4285	0.84 (0.66 – 1.06)	0.15

Nifedipine vs. Labetalol

	Nifedipine	Labetalol	Adjusted OR[a] (95% CI)	*p*
SGA < p10 - no PE	105 / 660	217 / 1232	0.96 (0.72 – 1.27	0.80
sHT	6 / 18	47 / 184	1.28 (0.39 – 3.82)	0.69
no sHT	97 / 605	169 / 1010	0.96 (0.71 – 1.31)	0.84

Data are n/N, SGA: Small for gestational age, OR: Odds ratio, CI: Confidence interval, PE: Preeclampsia, sHT: severe hypertension
[a] Adjusted for maternal age, parity, diabetes mellitus, socio-economic status, hypertension type, prior use of antihypertensives and comedication.

Supplementary table 2: Mean birth weights of subgroups

	Methyldopa (n=5900)	Labetalol (n=1391)	Nifedipine (n=695)	Polytherapy (n=987)
Subgroups				
Total	3057 ± 736	3134 ± 694.9	2933 ± 707	2786.3 ± 849
PIH	2960 ± 728	3059 ± 712	2899 ± 690	2581 ± 793
CH	3189 ±725	3180 ± 681	3043 ± 748	2863 ± 857
No PE	3157 ± 677	3181 ± 678	2946 ± 707	2931 ± 776
PE	2610 ± 818	2763 ± 720	2691 ± 654	2318 ± 907
No sHT	3150 ± 682	3208 ± 666	2922 ± 701	2981 ± 748
sHT	2706 ± 837	2829 ±732	2595 ± 787	2448 ± 909

Data are M±SD, M: Mean, SD: Standard deviation, PE: Preeclampsia, sHT: Severe hypertension PIH: Pregnancy-induced hypertension, CH: Chronic hypertension

Supplementary table 3: Oral antihypertensives and low birth weight

Labetalol vs. Methyldopa

	Labetalol	Methyldopa	Adjusted OR[a] (95% CI)	*p*
LBW	219 / 1389	1134 / 5867	0.88 (0.74 – 1.03)	0.11

Nifedipine vs. Methyldopa

	Nifedipine	Methyldopa	Adjusted OR[a] (95% CI)	*p*
LBW	191 / 693	1134 / 5867	1.58 (1.31 – 1.90)	<0.01

Nifedipine vs. Labetalol

	Nifedipine	Labetalol	Adjusted OR[a] (95% CI)	*p*
LBW	191 / 693	219 / 1389	1.98 (1.55 – 2.52)	<0.01

Data are n/N, LBW: Low birth weight, OR: Odds ratio, CI: Confidence interval,
[a] Adjusted for maternal age, parity, diabetes mellitus, socio-economic status, hypertension type, prior use of antihypertensives and comedication.

Supplementary table 4: Polytherapy vs. monotherapy SGA

	Polytherapy	Monotherapy	Adjusted OR[a] (95% CI)	*p*
SGA < p10 - Total	298/ 984	1594 / 7949	1.98 (1.69 – 2.30)	<0.01
PIH	104 / 268	1028 / 4427	2.05 (1.58 – 2.66)	<0.01
CH	194 / 716	566 / 3522	1.94 (1.60 – 2.34)	<0.01
No PE	200 / 751	1170 / 6692	1.91 (1.59 – 2.29)	<0.01
PE	98 / 233	424 / 1257	1.74 (1.28 – 2.36)	<0.01
No sHT	145 / 606	1031 / 5900	1.69 (1.38 – 2.08)	<0.01
sHT	110 / 275	407 / 1260	1.62 (1.21 – 2.15)	<0.01

Data are n/N, SGA: Small for gestational age, OR: Odds ratio, CI: Confidence interval, PIH: Pregnancy-induced hypertension, CH: Chronic hypertension, PE: Preeclampsia, sHT: severe hypertension
[a] Adjusted for maternal age, parity, diabetes mellitus, socio-economic status, hypertension type, prior use of antihypertensives and comedication.

Supplementary table 5: Abbreviations

aOR	Adjusted odds ratio
CH	Chronic hypertension
CI	Confidence interval
FGR	Fetal growth restriction
GA	Gestational age
HELLP	Haemolysis, elevated liver enzymes, low platelets (syndrome)
LBW	Low birth weight
M	Mean
PE	Preeclampsia
PIH	Pregnancy-induced hypertension
PPRN	PHARMO perinatal research network
RCT	Randomised-controlled trial
sHT	Severe hypertension
SD	Standard deviation
SES	Socioeconomic status
SGA	Small for gestational age