Does geographical location impact the efficacy of oral antihypertensive therapy in pregnancy?

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Abstract

To assess the efficacy of anti-hypertensive medications during pregnancy according to race, ethnicity and geographical location as current evidence is not clear in this regard. A subgroup meta-analysis of randomized controlled trials was performed. The efficacy of oral medications for chronic hypertension in pregnancy by geographical location [United States of America (USA) vs. rest of the World] was investigated. The location was used as a surrogate of racial identification and differences in health care systems and availability of medications that might affect the efficacy of the treatment. The number of patients in each group experiencing the following outcomes: small for gestational age (SGA), preeclampsia, severe hypertension were compared. Seven studies were identified. Subgroup analysis revealed that medications did not affect the occurrence of SGA. In six studies, therapies were protective for preeclampsia in the rest of the world but not in USA (p=0.02). Therapies were protective for severe hypertension. Our findings suggest that location does not affect the efficacy of medication in treating chronic hypertension during pregnancy. Geographical location may serve as a surrogate for genetic characteristics of a population of interest. However, it can also be influenced by other factors such as the heterogeneity of populations such as the USA. (J Turk Ger Gynecol Assoc. 2025; 26(2): 142-53)

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Introduction

Hypertensive disorders complicate approximately 10% of pregnancies worldwide with adverse maternal and fetal outcomes (1). Hypertension in pregnancy can be broadly categorized into four main conditions: chronic hypertension, gestational hypertension, preeclampsia, and eclampsia (2-4). Pharmacological management is traditionally based on beta blockers, calcium channel blockers and/or partial alpha blockers (1-3). In the case of non-pregnant women, there is a plethora of data, including randomized studies, showing the efficacy of antihypertensive agents in different racial groups (5,6). Using this extensive body of evidence, United Kingdom 2019 NICE guidelines (7) recommended when choosing antihypertensive drug treatment for adults of Black African or African-Caribbean family origin, an angiotensin II receptor

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blocker, in preference to an angiotensin-converting enzyme inhibitor. During pregnancy, non-Hispanic Blacks have a higher risk of pregnancy-induced hypertension and Asians/Pacific Islanders a lower risk of preeclampsia when compared to non-Hispanic White women (8).

A review from 2021 that included only randomized controlled trials (RCTs) in pregnant women, found only one trial that stratified outcomes of treated chronic hypertension by ethnicity (9). The only RCT that compared the use of oral nifedipine with labetalol for chronic hypertension during pregnancy according to the participants' ethnicity was published by Webster et al. (10). A total of 114 women with singleton pregnancies and a diagnosis of chronic hypertension were randomized to first-line antihypertensive therapy with either labetalol (n=56) or nifedipine (n=58). They found no difference in efficacy to reach the study's predetermined goal between the two medications overall and between Black and White individuals.

Given the availability of only one RCT in the literature on pregnant women regarding the efficacy of anti-hypertensive treatment during pregnancy according to ethnicity, we decided to use the location of the study as a surrogate for ethnicity of the patient. In addition, studying the effects of medical therapy according to geography allow us to factor in other influences towards the outcome, such as availability of health insurance for the general population, prevalence of comorbidities and other broad based baseline factors.

Material and Methods

We included RCTs on the efficacy of medications for chronic hypertension in pregnancy. We searched Medline, Embase, Scopus, Cochrane Library, the PROSPERO International Prospective Register of Systematic Reviews, and Google Scholar from July 20th, 1990, to July 20th, 2022.

We used the keywords "hypertension", "pregnancy", 'therapy" and "outcome". No language restrictions were applied. The references of related reviews and meta-analyses were searched manually. The following information was extracted from the complete manuscripts of the qualified studies: authors, location of the study, year of publication, number of patients treated with anti-hypertensive medication, and number of patients on placebo and/or aspirin. We divided the studies into subgroups according to the location of the study: United States of America (USA) vs. rest of the world. For each location the occurrence of outcomes were reported as follows: small for gestational age (SGA), preeclampsia, and severe hypertension. The definition of the outcomes are described in Table 1. These three outcomes were chosen based on clinical importance and because they were the most consistently collected outcomes in the included studies. For our analysis, patients on a different medication were considered to belong to a different study group.

Study selection

We included studies' medical therapy for the study group vs. placebo or aspirin in the control group. We excluded studies from which the data could not be extracted, such as case reports, reviews, meetings, letters, and surveys.

Data extraction

Two authors (B.M. and C.F.) conducted the study selection and independently screened the titles and abstracts to select potentially relevant citations for full text evaluation. When citations were considered relevant or when information in the title/abstract was insufficient for a decision on inclusion/exclusion criteria, the full text was retrieved and evaluated. In the event of discrepancies, a third reviewer was involved to help resolve conflicts and ensure accuracy.

Assessment of risk of bias

The risk of bias in each included study was assessed by using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (11,12). We used the risk-of-bias tool for randomized trials (Rob 2) tool structured into five domains of bias, according to the stages of a trial in which problems may arise: 1) the randomization process; 2) deviations from intended intervention; 3) missing outcome data; 4) measurement of the outcome; and 5) selection of the reported result (12). These categories were then used to assign an overall risk of bias for each of the articles considered in this meta-analysis. Review authors' judgments were categorized as "low-risk", "some concerns", or "high-risk" of bias. A proposed judgement about the risk of bias arising from each domain was generated. Two different authors assessed the risk of bias of all studies included in this review. In case of disagreement, a third reviewer adjudicated.

Statistical analysis

The data analysis was performed using Review Manager 5.4 (13) and R studio (14). Meta-analysis of adjusted and unadjusted risk ratios with 95% confidence intervals (CIs), using the Mantel-Haenszel method, was used to explore the association between anti-hypertensive therapy then pregnancy outcomes. A $p<0.05$ was considered statistically significant. We used the χ^2-based Cochran's Q test and Higgin'I^2 statistics to assess the degree of heterogeneity among studies. We considered an $I^2 \geq 50\%$ to be carrying considerable heterogeneity. If there was significant heterogeneity, the random-effects model was performed. Subgroup analyses were used to detect the contribution of each location (rest of the world vs. USA) to the outcome. In addition, we used the visualization of funnel plot and the relative Egger test to quantify the risk of publication bias. We considered an Egger test result with a $p>0.05$ as low risk of publication bias.

The institutional review board at the University of Arizona approved the study (approval number: STUDY00001570, date: 14.07.2022). We registered our protocol on PROSPERO, with registration number CRD42022348666, on August 8th, 2022.

Results

An initial search identified 3010 studies. However, out of these 3010 articles, only seven (0.2%) matched the inclusion and exclusion criteria.

Five studies were located in the "rest of the world" (15-19) and two studies were located in USA (20,21). All of them had data regarding SGA; six of them had data regarding preeclampsia and severe hypertension. We listed their definition of the outcomes and our interpretation for our analysis in Table 1, regarding each individual study.

Butters and Steyn (18) defined preeclampsia and severe hypertension according to the ISSHP criteria of 1988 (22) and they did not list the outcome severe preeclampsia.

Sibai et al. (20) did not specify the definition of preeclampsia, superimposed preeclampsia, and SGA; therefore, in our calculations, we interpreted their category term "superimposed preeclampsia" as belonging to our "preeclampsia" group, and their category "need for additional drugs to control severe hypertension" as belonging to the "severe hypertension group".

Tita et al. (21) defined preeclampsia and severe preeclampsia according to the American College of Obstetricians and Gynecologists (ACOG) criteria and referenced the ACOG

Table 1. Definitions of outcomes in the single studies

Authors, year, location	Definition of SGA	Definition of mild preeclampsia	Definition of severe preeclampsia	Definition of severe hypertension
Butters et al. (18)	BW <10th percentile	Data not present	Data not present	Data not present
Steyn et al. (19)	BW <10th percentile	ISSHP criteria of 1988*	Data not present	ISSHP criteria of 1988**
Vigil-De Gracia et al. (17)	BW <10th percentile	Data not present	New onset proteinuria with BP ≥160 mmHg systolic or ≥110 mmHg diastolic, or symptoms suggesting significant end-organ involvement	BP ≥160 mmHg systolic or ≥110 mmHg diastolic
Salama et al. (15)	BW <10th percentile	New onset proteinuria after 20 weeks of gestation	Data not present	BP ≥160 mmHg systolic or ≥110 mmHg diastolic
Rezk et al. (16)	BW <10th percentile	New onset proteinuria after 20 weeks of gestation	Data not present	BP ≥160 mmHg systolic or ≥110 mmHg diastolic
Sibai et al. (20)	Data present but definition not clarified	Data present but definition not clarified (it is called "superimposed preeclampsia" without further specifications)	Data not present	"Need for additional drugs to control severe hypertension"
Tita et al. (21)	BW <10th percentile	ACOG task force on Hypertension from 2013. They described the number of patients with "non-severe preeclampsia"	ACOG task force on Hypertension from 2013. They described the number of patients with "preeclampsia with severe features"	Worsening chronic hypertension
		They described the number of patients with "any preeclampsia" which is what we considered in our study		

*ISSHP criteria of 1988 for preeclampsia: single diastolic blood pressure measurement of 110 mmHg or more, or two consecutive measurements of 90 mmHg or more, at least 4 hours apart, without inclusion of the initial diastolic blood pressure or any systolic blood pressure value. Proteinuria is deemed to be important if it is more than 300 mg per 24 hour or 2+ on dipstick. **ISSHP criteria of 1988 for hypertension: single diastolic blood pressure measurement of 120 mmHg or more, or 2 consecutive measurement of 110 mmHg or more at least 4 hours apart. BP: Blood pressure, BW: Birth weight, SGA: Small for gestational age, ISSHP: International Society for the Study of Hypertension in Pregnancy, ACOG: American College of Obstetricians and Gynecologists

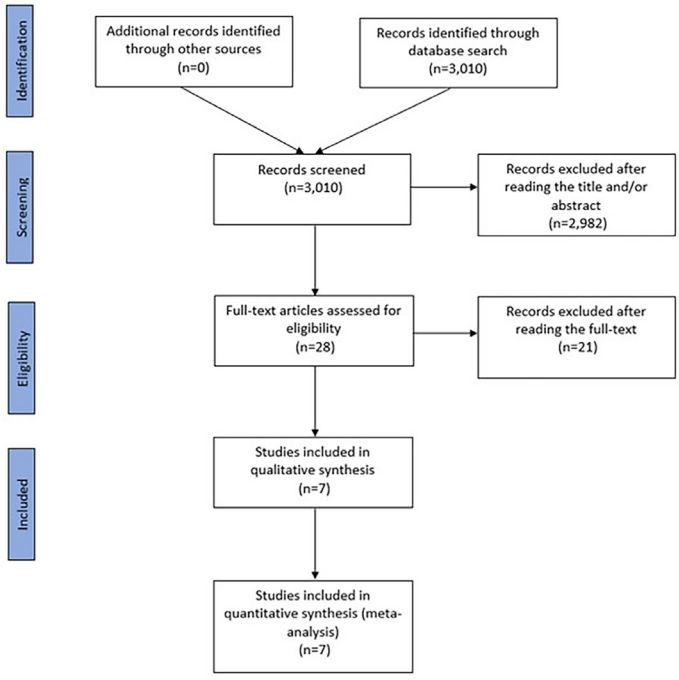


Figure 1. Flow chart of included/excluded studies

Table 2. Incidence of small for gestational age in the selected studies

Authors, year, location	Treatment type	Treatment (total)	SGA	No SGA	Comparator type	Comparator (total)	SGA	No SGA
Rest of the world								
Butters et al. (18)	Atenolol 50-200 mg daily	15	10	5	Placebo	14	0	14
Steyn et al. (19)	Ketanserin started at 40 mg per day % aspirin 75 mg per day*	69	7	62	Placebo + aspirin 75 mg per day**	69	9	60
Vigil-De Gracia et al. (17)	Amlodipine 5 mg a day	20	2	18	Aspirin 75 mg a day	19	2	17
	Furosemide 20 mg a day	21	1	20	Aspirin 75 mg a day	19	2	17
Salama et al. (15)	Methyldopa 1-2 gr per day + aspirin 81 mg per day	166	38	128	Placebo + aspirin 81 mg per day	164	32	132
	Nifedipine 20-40 mg per day + aspirin 81 mg per day	160	40	120	Placebo + aspirin 81 mg per day	164	32	132
Rezk et al. (16)	Labetalol 100-300 mg per day + aspirin 81 mg per day	160	66	94	Placebo + aspirin 81 mg per day	162	32	130
	Methyldopa 1-2 gr per day + aspirin 81 mg per day	164	34	130	Placebo + aspirin 81 mg per day	162	32	130
USA								
Sibai et al. (20)	Labetalol 300-2400 mg per day ± hydralazine 300 mg/day	86	7	79	Placebo	90	8	82
	Methyldopa 750 mg-4 gr per day ± hydralazine 300 mg/day	87	6	81	Placebo	90	8	82
Tita et al. (21)	Treatment (labetalol, nifedipine, amlodipine, methyldopa, HCTZ, other-data given only as aggregate)	1146	128	1018	Placebo	1124	117	1007

*Thirteen women in the ketanserin group needed additional antihypertensive medications - not specified which medications or outcomes for these. **Twenty-eight women in the placebo group needed additional antihypertensive medications - not specified which medications or outcome for these. SGA: Small for gestational age, USA: United States of America, HCTZ: Hydrochlorothiazide

task force on hypertension from 2013 (3); we grouped together the outcomes severe hypertension plus proteinuria, eclampsia, HELLP syndrome, and hypertension plus end-organ dysfunction. Moreover, they defined severe hypertension without preeclampsia as worsening chronic hypertension.

Regarding SGA there were 775 patients using anti-hypertensive medications and 773 patients using placebo/aspirin in the "rest of the world" group. In the USA group there were 1,319 patients using anti-hypertensive medications and 1,304 patients using placebo/aspirin Table 2.

Regarding mild preeclampsia in the "rest of the world" group, there were 760 patients using anti-hypertensive medications and 759 patients using placebo/aspirin, while in the USA group there were 1,381 patients using anti-hypertensive medications and 1,380 patients using placebo/aspirin Table 3.

The outcome of severe hypertension was reported for 760 patients using anti-hypertensive medications and 759 patients using placebo/aspirin in the "rest of the world" group. In the USA group 1,381 patients with severe hypertension using anti-hypertensive medications and 1,380 patients using placebo/aspirin Table 4.

The anti-hypertensive medications used were atenolol, ketanserin, amlodipine, furosemide, methyldopa, nifedipine, and labetalol. Tita et al. (21) did not specify exactly which medications they used, and have grouped several medications into one broad group.

Table 3. Incidence of preeclampsia in the selected studies

Authors, year, location	Treatment	Patient with antihypertensive drug	PE	No PE	Comparator type	Patients with no antihypertensive drug	PE	No PE
Rest of the world								
Steyn et al. (19)	Ketanserin started at 40 mg per day % aspirin 75 mg per day*	69	2	67	Placebo	69	13	56
Vigil-De Gracia et al. (17)	Amlodipine 5 mg a day	20	4	16	Aspirin	19	5	14
	Furosemide 20 mg a day	21	7	14	Aspirin	19	5	14
Salama et al. (15)	Methyldopa 1-2 gr per day + aspirin 81 mg per day	166	44	122	Placebo	164	80	84
	Nifedipine 20-40 mg per day + aspirin 81 mg per day	160	46	114	Placebo	164	80	84
Rezk et al. (16)	Labetalol 100-300 mg per day + aspirin 81 mg per day	160	48	112	Placebo	162	78	84
	Methyldopa 1-2 gr per day + aspirin 81 mg per day	164	50	114	Placebo	162	78	84
USA								
Sibai et al. (20)	Labetalol 300-2400 mg per day ± hydralazine 300 mg/day	86	14**	72	Placebo	90	14**	76
	Methyldopa 750 mg-4 gr per day ± hydralazine 300 mg/day	87	16**	71	Placebo	90	14**	76
Tita et al. (21)	Labetalol, nifedipine, amlodipine, methyldopa, HCTZ, others-data given only as aggregate	1208	295 (any preeclampsia)	913	Placebo	1200	373 (any preeclampsia)	827

*Thirteen women in the ketanserin group needed additional antihypertensive medications – not specified which medications or outcomes for these. **Their category term "superimposed PE" as belonging to our "PE" group. PE: Preeclampsia, USA: United States of America

Risk of bias of included studies

The "Rob 2" classification (12) showed that both studies had a low risk of bias (Table 5). The funnel plots are shown in Figures 3,4,6,7,9,10. The results of the Egger test (regression test for funnel plot asymmetry) were in accordance with the funnel plot "symmetry" and showed no evidence of publication bias.

Synthesis of results

Anti-hypertensives did not have any effect towards the occurrence of SGA in the US [relative risk (RR): 1.21, CI: 0.0.97-1.52] (Figure 2). Antihypertensives protected against preeclampsia in the rest of the world group (RR: 0.68, CI: 0.59-0.79) but not in the US where it did not reach statistical significance (RR: 0.85, CI: 0.67-1.09) (Figure 5).

Antihypertensives protected against the occurrence of severe hypertension (RR: 0.54, CI: 0.42-0.69) (Figure 8).

Discussion

Principal findings

Anti-hypertensive agents were not associated with an increased risk of SGA. In addition, they protected against preeclampsia and severe hypertension worldwide but not in the US where this effect did not reach statistical significance. We suggest that the reason why the USA differed in terms of preeclampsia is due to the year of the included studies (1990) which have likely biased the results-both studies from USA were done in 1990 while only 1 out of 5 studies from rest of the world was done in 1990-all the others were performed after 1990.

Comparisons with existing literature

Previous reviews and meta-analyses established the efficacy of antihypertensives during pregnancy but only one RCT by Webster et al. (23), analyzed the occurrence of poor pregnancy outcomes according to the ethnicity of the patient. They compared treatment with oral nifedipine and labetalol for chronic hypertension during pregnancy according to the participants' ethnicity. A total of 114 women with singleton pregnancies and a diagnosis of chronic hypertension were randomized to first-line anti-hypertensive therapy with either labetalol (n=56) or nifedipine (n=58). They found no difference in efficacy to reach the goal of the study between the two medications overall and between Black and White individuals.

Other meta-analyses were performed in regard of this topic earlier, but with key differences from our study. Bellos et al. (24) in 2020 included in the same analysis 22 RCTs and observational studies, while we included only RCTs. Particularly, they did not analyze the race/ethnicity of the patients. Al Khalaf et al. (25) performed a meta-analysis of 16 studies on anti-hypertensive treatment during pregnancy. They did not find any difference of interest regarding maternal race/ethnicity on pregnancy

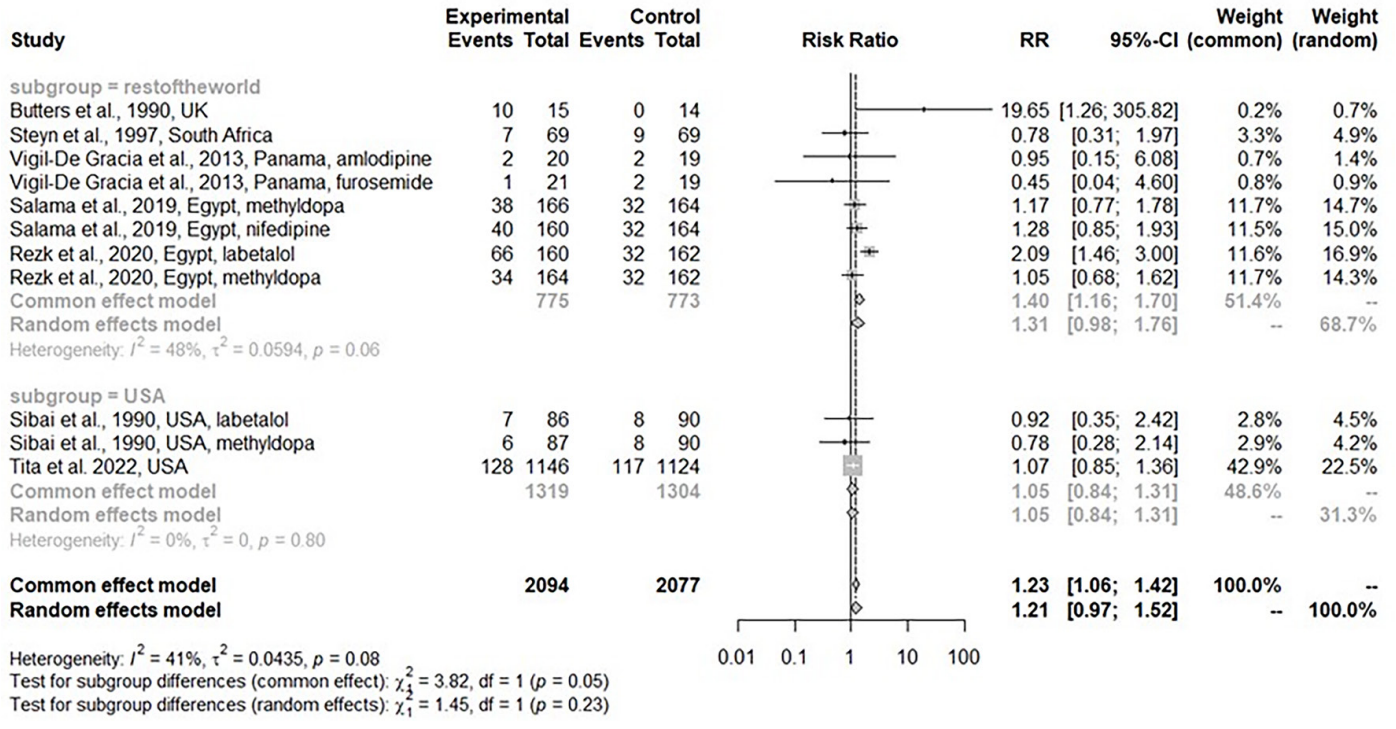


Figure 2. Forest plot of risk ratio of occurrence of small for gestational age via the meta-analytic method
RR: Risk ratio, CI: Confidence interval

outcomes. However, they included only observational studies while we included only RCTs. Bone et al. (26) performed a meta-analysis of 61 RCTs using oral antihypertensives for non-severe pregnancy hypertension, including all pregnancy hypertension types, while we focused only on chronic hypertension. They did not analyse the race/ethnicity of the patients.

Instead of dividing the patients per ethnicity, we divided the patients by location of the study.

In the present study factors other than ethnicity played a role, such as broader socio-economic determinants of health, including medical insurance coverage and comorbidities. The lack of difference in terms of outcomes in our subgroups for most of the included pathologies is similar to the results found

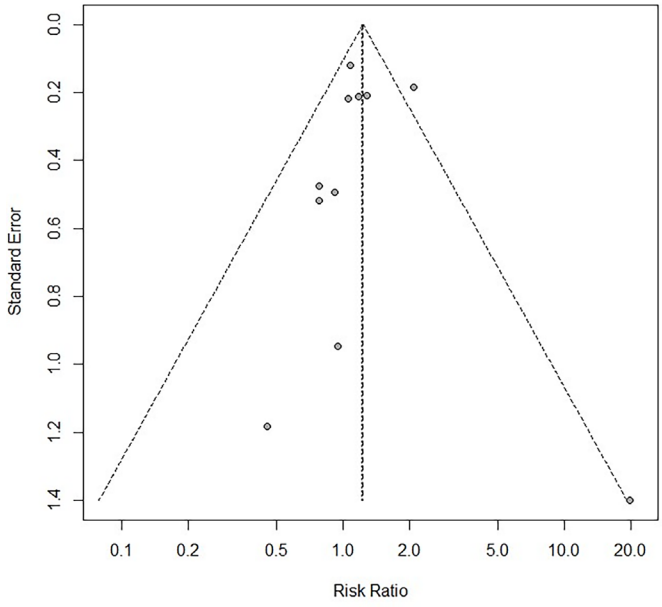


Figure 3. Funnel plot of standard error (symmetry/asymmetry risk of bias evaluation) considering small for gestational age as outcome

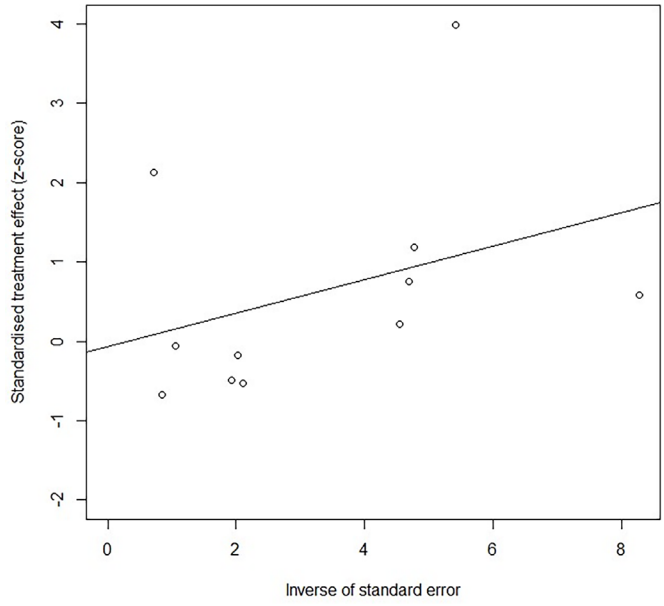


Figure 4. Linear regression test of funnel plot asymmetry for small for gestational age (p=0.9257, indicating no evidence of publication bias)

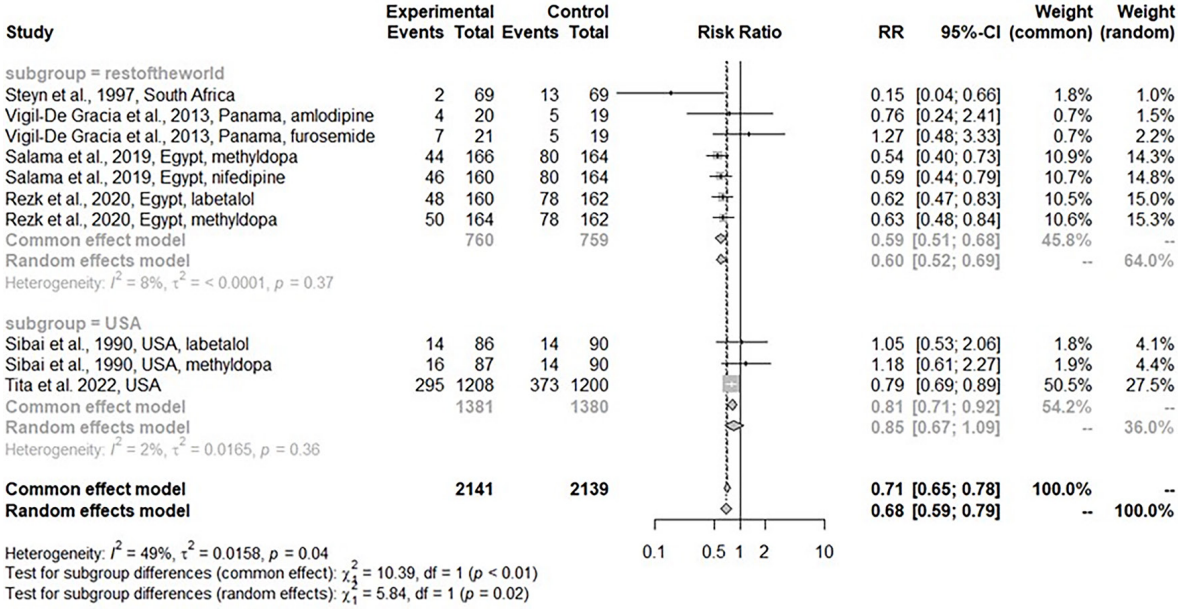


Figure 5. Forest plot of risk ratio of occurrence of preeclampsia via the meta-analytic method
RR: Risk ratio, CI: Confidence interval

by Webster et al. (27), pointing towards a hypothesis of equal efficacy of anti-hypertensive medications worldwide and in populations that are ethnically, socially and economically different.

Webster et al. (27) included RTCs published before November 2016, therefore excluding some more recent important large trials. They found 15 RCTs and they did not analyse the race/ethnicity of the patients. None of the previous studies stratified the outcomes based on the location of the study.

Study limitations

No previous study performed a subgroup analysis by location of the study. Our meta-analysis had strict inclusion criteria, including only RCTs and only women diagnosed with chronic hypertension. The limitations of the meta-analysis are the different drugs used and the high heterogeneity of the studies. In addition, the inclusion of studies from every year biased our study, indeed two out of seven studies were performed in the 1990s when the medications available and the health systems were drastically different from the present age (18,20).

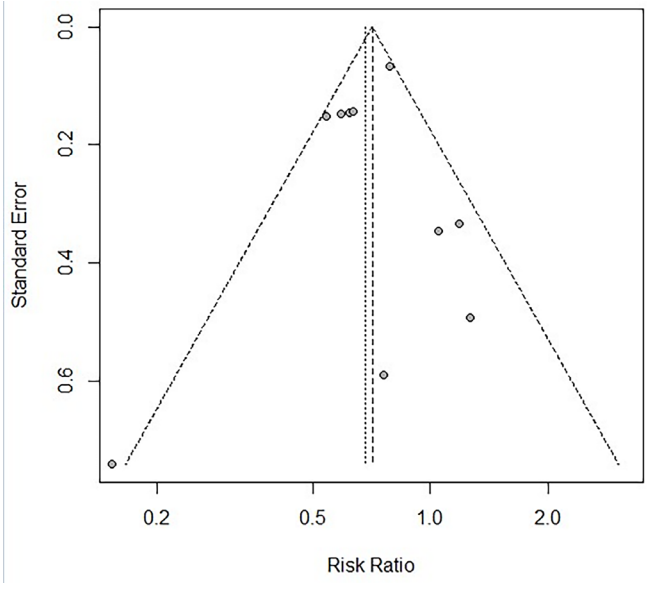


Figure 6. Funnel plot of standard error (symmetry/asymmetry risk of bias evaluation) considering preeclampsia as outcome

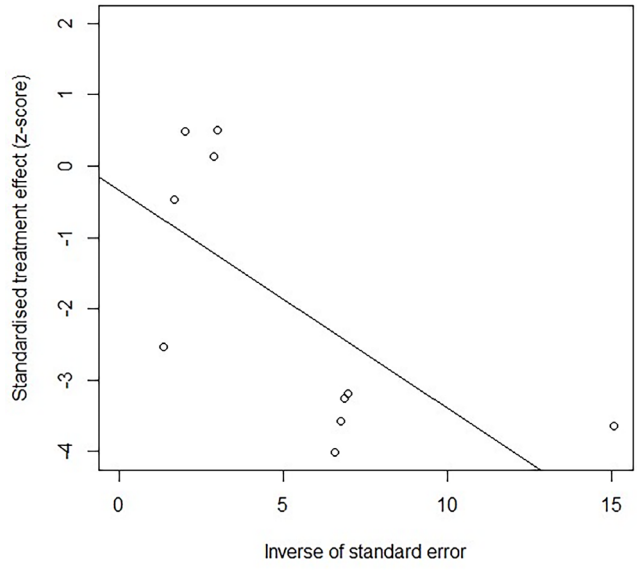


Figure 7. Linear regression test of funnel plot asymmetry for preeclampsia (p=0.6847, indicating low-risk of publication bias)

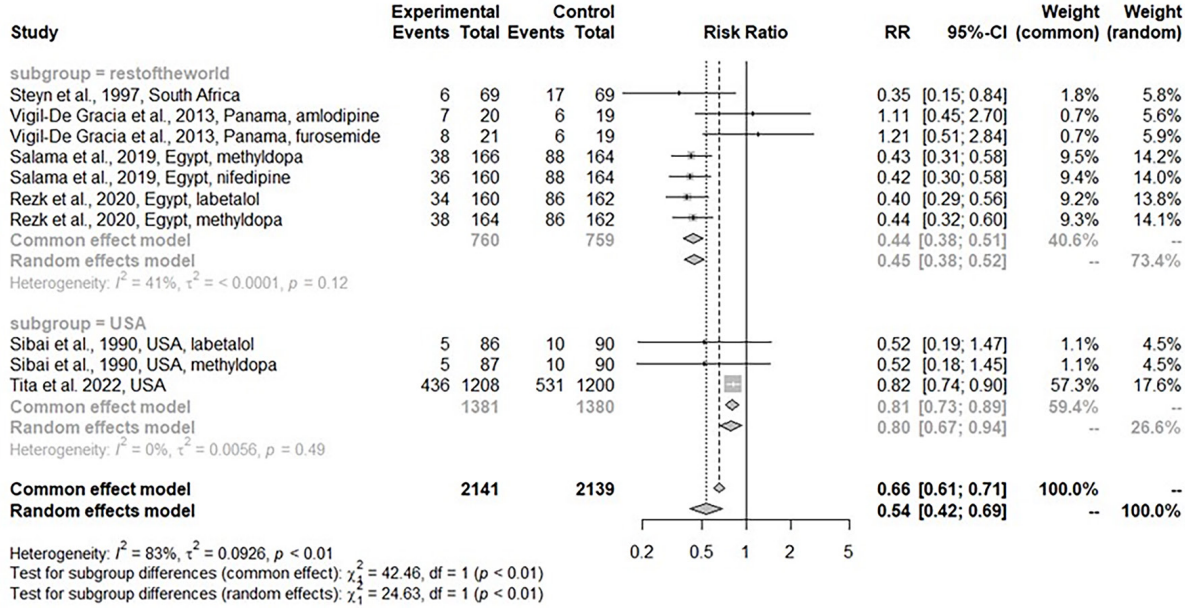


Figure 8. Forest plot of risk ratio of occurrence of severe hypertension via the meta-analytic method
RR: Risk ratio, CI: Confidence interval

Table 4. Incidence of severe hypertension in the selected studies

Authors, year, location	Treatment	Patient with antihypertensive drug	Severe hypertension	Non-severe hypertension	Comparator (type)	Patients with no antihypertensive drug	Severe hypertension	Non-severe hypertension
Rest of the world								
Steyn et al. (19)	Ketanserin started at 40 mg per day % aspirin 75 mg per day*	69	6 (severe hypertension ISSHP 1988)	63	Placebo	69	17 (severe hypertension ISSHP 1988)	52
Vigil-De Gracia et al. (17)	Amlodipine 5 mg a day	20	7	13	Aspirin	19	6	13
	Furosemide 20 mg a day	21	8	13	Aspirin	19	6	13
Salama et al. (15)	Methyldopa 1-2 gr per day + aspirin 81 mg per day	166	38	128	Placebo	164	88	76
	Nifedipine 20-40 mg per day + aspirin 81 mg per day	160	36	124	Placebo	164	88	76
Rezk et al. (16)	Labetalol 100-300 mg per day + aspirin 81 mg per day	160	34	126	Placebo	162	86	76
	Methyldopa 1-2 gr per day + aspirin 81 mg per day	164	38	126	Placebo	162	86	76
USA								
Sibai et al. (20)	Labetalol 300-2400 mg per day ± hydralazine 300 mg/ day	86	5**	81	Placebo	90	10**	80
	Methyldopa 750 mg-4 gr per day ± hydralazine 300 mg/day	87	5**	82	Placebo	90	10**	80
Tita et al. (21)	Treatment (labetalol, nifedipine, amlodipine, methyldopa, HCTZ, other - data given only as aggregate)	1208	436 (severe hypertension)	772	Placebo	1200	531 (severe hypertension)	669

*Thirteen women in the ketanserin group needed additional antihypertensive medications - not specified which medications or outcomes for these. **Need for additional drugs to control severe hypertension" as belonging to the "severe preeclampsia group". ISSHP: International Society for the Study of Hypertension in Pregnancy, HCTZ: Hydrochlorothiazide

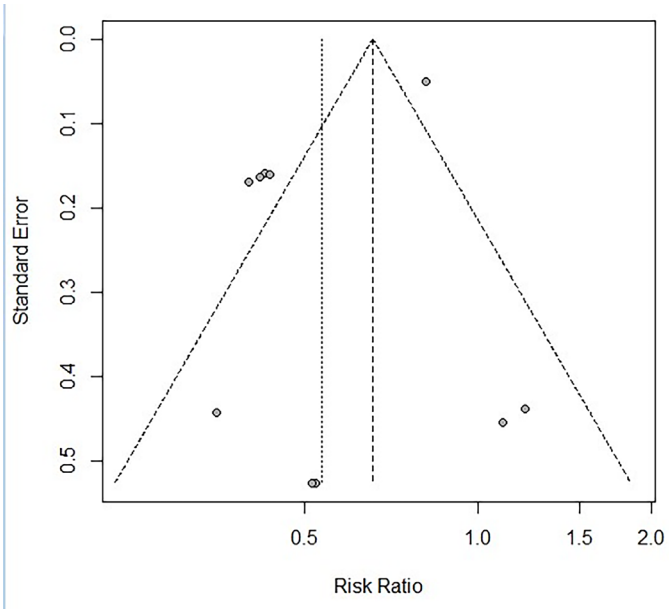


Figure 9. Funnel plot of standard error (symmetry/asymmetry risk of bias evaluation) considering severe hypertension as outcome

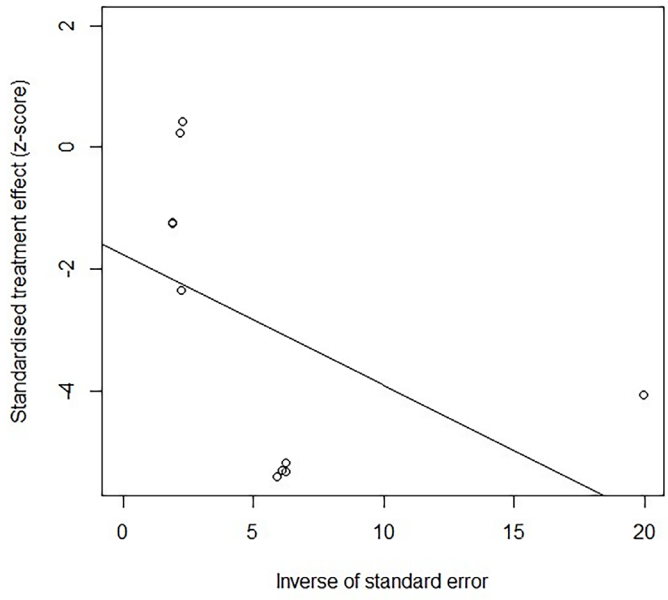
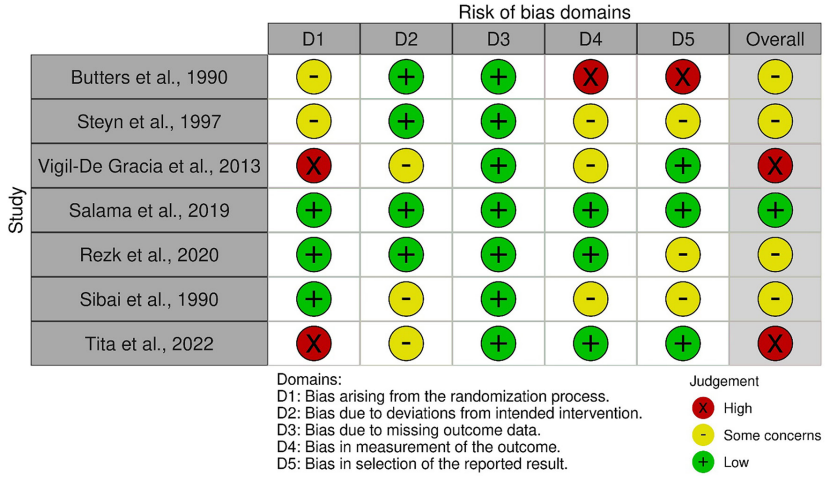


Figure 10. Linear regression test of funnel plot asymmetry for severe hypertension (p=0.1208, indicating no evidence of publication bias)



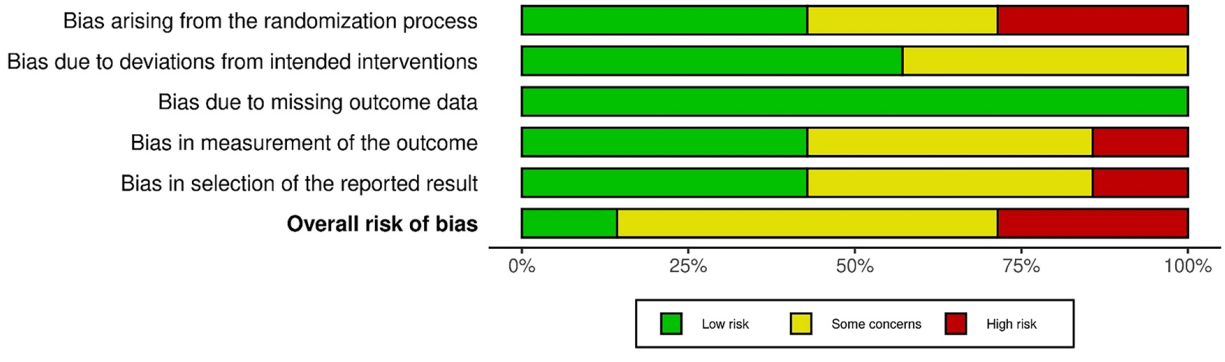


Table 5. Risk-of-bias tool for randomized trials (Rob) 2 assessment for selected studies.
D1: Bias arising from the randomization; process, D2: Bias due to deviations from the intended interventions, D3: Bias due to missing outcome data, D4: Bias in measurement of the outcome, D5: Bias in selection of the reported result

Conclusion

There seems to be no differences according to location, regarding the efficacy of medication in treating chronic hypertension during pregnancy. Geographical location could serve as a surrogate for genetic characteristics of a population of interest. However, it can be influenced by other factors such as heterogeneity of the ethnicity of the national population (e.g. USA), variation in healthcare systems and class of medications used (28,29).

We do not know how much of this is the result of the health system/availability of private vs. public insurance, ethnicity, and other baseline population characteristics. Therefore, we suggest conducting trials with outcome according to ethnicity and other baseline characteristics.

Footnotes

Author Contributions: *Design: A.S., G.S., Data Collection or Processing: B.A., C.F., Analysis or Interpretation: A.S., G.S., Literature Search: B.A., C.F., Writing: D.E., B.A., Critical Review: A.S., G.S., P.D.F.*

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