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ANTIHYPERTENSIVE MEDICATIONS IN PREGNANCY: A SYSTEMATIC REVIEW OF EFFICACY, SAFETY, AND CLINICAL GUIDANCE

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ABSTRACT

Hypertension affects a growing number of reproductive-age women, posing risks during pregnancy. This systematic review synthesizes evidence on antihypertensive efficacy, safety, and guidance, drawing from a cohort of 1,641 HDP patients and broader literature. Key findings highlight beta-blockers and methyldopa as safe first-line options for chronic and gestational hypertension, with calcium channel blockers as alternatives. RAAS inhibitors are contraindicated due to fetal harms. Management involves BP control to 110–140/85 mmHg, preeclampsia screening, and fetal monitoring. Guidelines stress pre-conception drug switching from teratogens. Outcomes vary by HDP type, with treated patients showing demographic differences. This underscores the need for tailored, multidisciplinary approaches to improve maternal-fetal health.

KEYWORDS: Hypertension, Pregnancy, Antihypertensives, Preeclampsia, Safety, Efficacy, Guidelines, Methyldopa, Labetalol, RAAS inhibitors.

INTRODUCTION

The rate of hypertension continues to rise dramatically; almost 8% of women of reproductive age (22–44 year) are affected by hypertension in the USA.[1] The incidence of hypertension prior to pregnancy among 15 54-year-old women increased 2-fold from 1993 to 2002 (from 12.3 to 28.9 per 1000 deliveries). Pregnancy-associated hypertension remains an important cause of maternal and fetal morbidity and mortality.[2] and more evidence has confirmed that pregnancy-associated hypertension could cause early childhood cardio-metabolic disorder.[3][4] The majority of women with controlled-chronic hypertension under appropriate management will have successful outcomes, however, pre-pregnancy hypertensive women with poorly-controlled blood pressure in the first trimester have significantly increased risk of target organ damage in both mothers and foetuses, low birth weight, pre-eclampsia and other adverse outcomes. Most current guidelines and clinical trials focus on the management and treatments for hypertension during pregnancy and breast-feeding, while limited evidence could be applied to the management of hypertension before pregnancy.

2. MATERIALS AND METHODS

2. A Study population

This retrospective, observational cohort study utilized a previously assembled dataset consisting of pregnant individuals with new onset HDP who delivered at the University of North Carolina at Chapel Hill (UNC-Chapel Hill) or Duke University between 2007 and 2017 (Supplementary Figure S1). Women with an International Classification of Disease (ICD) 9 or 10 diagnosis code for HDP from an inpatient or outpatient encounter were included (N = 9,782). In women with multiple pregnancies complicated with HDP, the first pregnancy served as the index pregnancy. Individuals with an HDP diagnosis greater than 6 months prior to or 6 weeks after delivery date (N = 552), an invalid gestational age or delivery before Epic electronic health records (EHR) implementation at each site in 2014 (N = 3,623), and no medication data available during pregnancy or on the date of delivery (N = 3,966) were excluded. The remaining 1,641 patients were included in the final dataset for analysis. This study was approved by the institutional review boards at Duke University and UNC-Chapel Hill.

2. B Data collection

Demographic characteristics collected from the EHR included race, ethnicity, age, insurance status, site of delivery, and year of delivery. Significant past medical history (history of hypertension, hyperlipidemia, diabetes mellitus, and renal disease) and pregnancy characteristics (gestational age of onset of HDP, gestational diabetes) were also collected. Race and ethnicity were based on self-report as recorded in the EHR. Race was classified as White, Black, or Other (defined as Pacific Islander, Native American, or unknown race), and ethnicity was classified as Hispanic or Not Hispanic. HDP type was classified based on diagnoses codes from ICD-9 (642.5: severe preeclampsia, 642.7: preeclampsia or eclampsia superimposed on pre-existing hypertension) and ICD-10 (O11: pre-existing hypertension with preeclampsia, O13: gestational hypertension without significant proteinuria, O14: preeclampsia, O15: eclampsia). HDPs were ranked in order of increasing severity: gestational hypertension, preeclampsia, chronic hypertension with superimposed preeclampsia, and severe preeclampsia including eclampsia.

The primary endpoint was treatment with an antihypertensive medication (yes/no) at any inpatient or outpatient encounter during pregnancy and/or on the date of delivery. Among the patients that received treatment, medication class (beta blocker, calcium channel blocker, vasodilator, alpha agonist, diuretic) was a co-primary endpoint. Specific medications within the medication classes (e.g., labetalol, nifedipine, hydralazine, methyldopa, hydrochlorothiazide) and the number of antihypertensive medication classes used (one, two, three or more) were secondary endpoints.

2. C Data analysis

Baseline characteristics and the frequency of the primary endpoints were described in the overall study population, and compared across HDP type (eclampsia/severe preeclampsia, chronic hypertension with superimposed preeclampsia, preeclampsia, and gestational hypertension), by descriptive statistics. An analysis conducted exclusively within the subset of 1,276 patients treated with an antihypertensive medication compared the medication class and individual medication endpoints across HDP type. A Chi-square test was used to determine whether differences in the proportion of the primary and secondary endpoints existed across HDP diagnosis categories. To account for implementation of ICD-10 codes for diagnosing HDP in October 2015, a sensitivity analysis describing the frequency of

antihypertensive use and selection across HDP type was conducted solely within patients who delivered in 2016 and 2017.

In order to identify demographic and clinical factors associated with the use and selection of antihypertensive medications, demographic and clinical factors were compared across those treated versus not treated and those treated versus not treated with the most commonly ordered classes of agents (beta blockers, calcium channel blockers, vasodilators). We evaluated whether differences in each factor existed across medication groups (yes/no) using Chi-square or Student's t-test, as appropriate, and determined the magnitude of the associations utilizing logistic regression. Unadjusted odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated to determine whether each demographic and clinical factor was associated with each medication endpoint [treatment with any antihypertensive, medication classes used (beta blocker, calcium channel blocker, vasodilator)]. To determine which factors were independently associated with antihypertensive use (yes/no), beta blocker use (yes/no), calcium channel blocker use (yes/no), and vasodilator use (yes/no), adjusted ORs and 95% CIs were also calculated for each demographic and clinical factor in a multivariate logistic regression model for each endpoint. The data for this cohort was analyzed with SAS-JMP Pro v15.2. P-values <0.05 were considered statistically significant.

2. D RESULTS

Demographic and clinical characteristics of the total study population

The demographic and clinical characteristics of the study population (N = 1,641) are described in Table 1. The mean (±SD) age of the population was 30.5 ± 6.5 years, and 41.0% patients self-identified as Black race and 15.7% patients self-identified as Hispanic. In addition, 30.5% of patients had a history of hypertension, defined as chronic hypertension within 12 months of delivery. The distribution of HDP type was 289 (17.6%) patients with eclampsia/severe preeclampsia, 557 (33.9%) with preeclampsia, 401 (24.4%) with chronic hypertension with superimposed preeclampsia, and 394 (24.0%) with gestational hypertension.

Table 1
Demographics of the study population.

	Female (N = 75)	Male (N = 24)	Total (N = 99)	Test value	p-value
Age (in years)				2.38	.126
Mean (*SD*)	26.56 (9.36)	30.04 (10.42)	27.40 (9.69)		
Range	16.00–56.00	18.00–58.00	16.00–58.00		
Handedness (EHI)				0.70	.703
left hander	7 (9.3%)	2 (8.3%)	9 (9.1%)		
mixed hander	7 (9.3%)	1 (4.2%)	8 (8.1%)		
right hander	61 (81.3%)	21 (87.5%)	82 (82.8%)		
Paranoid Belief Scores (PDI)					
Number of Paranoid Beliefs				4.26	.042
Mean (*SD*)	3.21 (2.48)	4.62 (4.00)	3.56 (2.96)		
Range	0.00–10.00	0.00–15.00	0.00–15.00		
Conviction (weighted)				2.93	.090
Mean (*SD*)	2.07 (1.18)	2.56 (1.31)	2.19 (1.22)		
Range	0.00–4.00	0.00–5.00	0.00–5.00		
Distress (weighted)				0.63	.429
Mean (*SD*)	1.55 (0.97)	1.38 (0.68)	1.50 (0.90)		
Range	0.00–4.00	0.00–3.00	0.00–4.00		
Preoccupation (weighted)				0.66	.419
Mean (*SD*)	1.57 (0.93)	1.74 (0.87)	1.61 (0.92)		
Range	0.00–3.75	0.00–3.50	0.00–3.75		
Total Score (weighted)				0.66	.419
Mean (*SD*)	6.03 (3.10)	6.60 (2.64)	6.17 (2.99)		
Range	0.00–12.50	0.00–10.50	0.00–12.50		

Table No. 1: Demographic and clinical factors in total study population compared across HDP type.

Various differences in the demographic and clinical characteristics were observed across HDP type (Table 1). Individuals diagnosed with eclampsia/severe preeclampsia were diagnosed with HDP earlier in the pregnancy, were younger in age, and had a lower prevalence of diabetes compared to other HDP types. Patients diagnosed with chronic hypertension with superimposed preeclampsia were older, and contained a higher proportion of Black patients, patients with a known history of hypertension, and patients with a history of renal disease.

3-**Classification of hypertension and medication given during that stages**

3. A Chronic hypertension

Chronic hypertension predates the pregnancy or is first diagnosed before 20 weeks gestation. It includes both primary hypertension and less commonly secondary hypertension, related to an underlying cause, such as kidney disease. Routine testing for secondary causes is not recommended in pregnancy, but should be considered postpartum. For pregnant women with chronic hypertension, the initial recommended tests are.[5-7]

- full blood count
- urea, creatinine and electrolytes
- liver function tests
- uric acid
- urinalysis and microscopy
- urine protein: creatinine ratio (to establish a baseline)
- ECG.

Chronic hypertension is associated with adverse maternal and fetal outcomes:

- superimposed pre-eclampsia – 25%
- preterm delivery – 28%
- fetal growth restriction – 17%
- perinatal death – 4%.(8).

Some women have white-coat hypertension. This is defined as a clinic blood pressure of at least 140/90 mmHg, but with normal blood pressure outside the clinic. It is diagnosed by 24-hour ambulatory blood pressure monitoring or home blood pressure monitoring. White-coat hypertension is not entirely benign and is associated with an increased risk of pre-eclampsia (8%).[9] Generally, treatment is not required if the clinic blood pressure is below 160/110 mmHg and the out-of-office blood pressure remains normal.

MANAGEMENT

Women with chronic hypertension may be taking antihypertensive drugs before conception or conceive while taking them. Some of these drugs are contraindicated or not recommended in pregnancy (Table 1).(9) Table 2 lists oral antihypertensive drugs that are safer in pregnancy.[6,10]

Table No. 1: Antihypertensive drugs to avoid in pregnancy.

Antihypertensive class	Advice	Potential adverse effects	Recommendation
ACE inhibitors	Contraindicated	Teratogenic in the second and third trimester resulting in fetal anuria, oligohydramnios, hypocalvaria, intrauterine growth restriction and patent ductus arteriosus, death	Stop drug ideally before conception or at diagnosis of pregnancy
Angiotensin receptor blockers	Contraindicated	Teratogenic in the second and third trimesters, fetal anuria, oligohydramnios, hypocalvaria, intrauterine growth restriction, patent ductus arteriosus, death	Stop drug ideally before conception or at diagnosis of pregnancy
Diuretics	Avoid	Maternal hypovolaemia, fetal hypoglycaemia, thrombocytopenia, hyponatraemia and hypokalaemia	Use an alternative antihypertensive
Beta blockers (other than labetalol)	Avoid	Fetal bradycardia, intrauterine growth restriction (atenolol)	Use an alternative antihypertensive
Calcium channel antagonists (other than nifedipine and diltiazem)	Avoid	Maternal hypotension and fetal hypoxia	Use an alternative antihypertensive

Table No. 2: Antihypertensive drugs that can be safely used in pregnancy.

Antihypertensive drug*	Class/action	Dose	Adverse effects
Labetalol	Beta blocker	100 mg twice a day – 400 mg three times a day	Bradycardia, bronchospasm, headache
Nifedipine controlled release	Calcium channel antagonist	30 mg daily – 60 mg twice a day	Headache (first-dose effect), flushing, tachycardia, peripheral oedema
Methyldopa	Central action	250 mg twice a day – 750 mg three times a day	Depression, dry mouth, sedation, rarely haemolysis and hepatitis
Hydralazine	Vasodilator	25 mg three times a day – 50 mg three times a day	Flushing, headache, lupus-like syndrome
Prazosin	Alpha blocker	0.5 mg twice a day – 5 mg three times a day	Orthostatic hypotension

The mainstay of management of chronic hypertension in pregnancy is regular maternal review and strict blood pressure control. Often the physiological fall in blood pressure in the first trimester will allow for a reduction or cessation of antihypertensive drug therapy.

Optimal management includes maintaining the blood pressure around 110–140/85 mmHg, regular assessment for the development of pre-eclampsia and close surveillance of fetal growth and wellbeing. Signs and symptoms suggestive of pre-eclampsia include headache, visual changes, epigastric or right upper quadrant pain and oedema (see Box). Assessment also includes careful blood pressure measurement, ideally using automated office or a liquid crystal sphygmomanometer, and testing for proteinuria. Home blood pressure monitoring may form part of this assessment. Proteinuria is defined as a spot urine protein:creatinine ratio above 30 mg/mmol or urine protein excretion above 300 mg/24 hours. Dipstick urinalysis (automated or visual) is most commonly used to screen for proteinuria, with a ‘negative’ or ‘trace’ result being normal. One plus (1+) or more on dipstick is sensitive, but inaccurate and should be further evaluated with a spot urine protein:creatinine ratio.

3. B Gestational hypertension

Gestational hypertension is the development of hypertension at or after 20 weeks gestation, in the absence of other features of pre-eclampsia (see Box). Gestational hypertension is associated with an increased risk of developing pre-eclampsia (up to 25%, depending on the gestation at presentation), as well as the future development of cardiovascular disease.[5-7]Fetal growth restriction is not typically a feature of gestational hypertension. Box - Features of pre-eclampsia and eclampsia

Renal

- proteinuria – spot urine protein:creatinine ratio 30 mg/mmol or more
- acute kidney injury with serum creatinine >90 micromol/L
- oliguria: <80 mL/4 hours.

Hematological

- thrombocytopenia – platelet count <100,000/microlitre
- haemolysis
- disseminated intravascular coagulation.

Hepatic

- raised serum transaminases (alanine aminotransferase or aspartate aminotransferase >40 IU/L)
- severe right upper quadrant or epigastric pain.

Neurological

- eclamptic convulsion
- sustained clonus (hyperreflexia is commonly found and not diagnostic)
- severe headache
- visual disturbance – photopsia, scotomata, cortical blindness
- stroke
- Uteroplacental dysfunction with fetal growth restriction, abnormality on doppler imaging of the umbilical artery, stillbirth.

MANAGEMENT

Regular blood pressure monitoring is necessary to ensure the blood pressure remains at 110–140/80–90 mmHg. There should be regular assessment for the development of pre-eclampsia and close surveillance of fetal growth and wellbeing. Once the blood pressure is controlled, gestational hypertension may continue to be managed with outpatient care, under close and regular.

3. C Pre-eclampsia

Pre-eclampsia is a complex multisystem disorder of pregnancy arising from abnormal placentation, resulting in an imbalance of angiogenic and anti-angiogenic factors, oxidative stress and immunological involvement. The maternal response to this is thought to involve

systemic vascular endothelial dysfunction. Pre-eclampsia may be superimposed on chronic hypertension, or present as new onset hypertension, arising at or after 20 weeks gestation, with the presence of one or more of the typical clinical features (see Box).[5-6]

Risk factors for pre-eclampsia include maternal age, primiparity, previous pre-eclampsia, multiple gestation, prolonged interpregnancy interval and assisted reproduction therapies. Other factors are underlying renal disease or hypertension, antiphospholipid syndrome, systemic lupus erythematosus, diabetes and a maternal body mass index (BMI) above 30 kg/m2.

Adverse maternal outcomes include eclampsia, stroke, multiorgan failure, major haemorrhage and death. Fetal complications of pre-eclampsia include growth restriction, preterm delivery, placental abruption and perinatal death.

MANAGEMENT

Whether pre-eclampsia is new onset or superimposed on chronic hypertension, a multidisciplinary approach optimises maternal and fetal outcomes as delivery is the only definitive cure. There is a balance between the welfare of the growing fetus and the ongoing risk of maternal complications. Management should occur at a specialist centre with the required protocols and expertise because inpatient care is usually required.

For severe hypertension urgent management is indicated and drugs are required to rapidly lower blood pressure (Table 3). An infusion of magnesium sulphate can be considered as it reduces the rate of seizure by 50% (Table 4).[11]

Table 3: Urgent treatment of severe hypertension* in pregnancy.

Drug	Dose	Route	Onset of action	Adverse effects
Hydralazine	5–10 mg	Intravenous bolus repeated after 20 min if blood pressure remains >160/110 mmHg	20 min	Flushing, headache, nausea, hypotension, tachycardia
Labetalol	20–80 mg	Intravenous bolus over 2 min, repeat after 10 min if blood pressure remains >160/110mmHg	5 min	Bradycardia, hypotension, fetal bradycardia
Labetalol	200 mg	Oral	30–45 min	Bradycardia, bronchospasm, headache
Nifedipine†	10 mg	Oral	30–45 min	Headache, flushing

Table No. 4: Seizure prophylaxis and treatment of eclampsia. Severe hypertension is 160/110 mmHg or above.

Drug	Dose	Route	Onset of Action	Adverse effects
Magnesium	4 g	Intravenous bolus over 20 min followed by 1 g/hour infusion, typically continued for 24 hours	20 min	Flushing, respiratory depression Caution in renal impairment as magnesium is excreted renally and toxicity may occur

3. D Drugs for mild HTN

Beta-blockers

Beta-blockers (BB) are first-line medication during pregnancy and lactation. Labetalol is one of the commonest drugs used in HDP. It can be used parenterally in cases of severe HTN. BB may cause foetal bradycardia or intrauterine growth retardation; thus, proper monitoring of the foetus is essential. Atenolol is better avoided during pregnancy.[12]

Alpha methyldopa

This is an α2-adrenergic agonist that has central nervous system (CNS) and peripheral nervous system effects. It is one of the safest drugs during pregnancy; been used for more than 40 years, with no serious side effects on the mother or the foetus, although it has been largely displaced by labetalol as the first-line agent of choice for most patients. The recommended daily dose of methyldopa is 0.5–3.0 g in 2–4 doses. Side-effects include sleepiness, dry mouth, general malaise, haemolytic anaemia, and hepatopathy.[13]

Calcium channel blockers

Calcium channel blockers (CCBs) are among the recommended antihypertensive drugs during pregnancy. Both dihydropyridines and non-dihydropyridines are allowed.[12]

Diuretics

The use of diuretics during pregnancy carries a potential risk of oligohydramnios. Unless there is a compelling indication for the use of diuretics (e.g., heart failure), their use is not recommended. Diuretic therapy is better avoided in pre-eclampsia because the plasma volume is contracted.[12] Only loop diuretics are allowed, while thiazide and potassium-sparing diuretics are contraindicated during pregnancy.

Renin-angiotensin-aldosterone system inhibitors

Renin-angiotensin-aldosterone system (RAAS) inhibitors include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), renin inhibitors, non-selective (spironolactone) and selective (eplerenone) aldosterone antagonists.

Recent studies suggest that exposure early in pregnancy during the period of organogenesis does not confer an increase in the risk of malformations.[14] However, animal and human data suggest that RAAS inhibitor use during the second and third trimesters is associated with a higher risk of complications, including renal dysplasia, pulmonary hypoplasia, and growth restriction.[15]

The guidelines recommend against the use of RAAS inhibitor drugs during pregnancy and lactation (Class III recommendations). Beta-blockers are used as an alternative to ACEIs and ARBs in younger hypertensive women planning pregnancy.[16]

4-Guidelines for pre-pregnancy hypertension treatment

Most guidelines gave the pre-pregnancy antihypertensive advice based on the evidence from pregnancy chronic hypertension guidelines. Internationally, the guidelines vary for the management of chronic hypertension during pregnancy. It must be stressed that none of the many antihypertensive agents used in routine practice have been shown to be teratogenic to be taken safely (Table 5). The majority of the guidelines recommend that women on angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) and planning to become pregnant have to discuss with their doctor prescription of an alternative.[17] Antihypertensive treatment should be discontinued in women taking ACE inhibitors or ARBs if they become pregnant (preferably within two working days of notification of pregnancy) as ACE inhibitors and ARBs are teratogenic, with increased risk of congenital abnormalities if taken during early pregnancy, and they are therefore contraindicated.[18-21]

Methyldopa is often considered the first-line therapy for pre-pregnancy antihypertensive treatment [22,23] with the largest quantity of data regarding fetal safety since it has been used for pregnancy hypertension since 1960s.[24] even in the first trimester.[25] In a 7.5-year follow-up study, there were no adverse growth or developmental outcomes in children whose mothers received methyldopa during pregnancy.[26]Many clinicians opt to change women's antihypertensive therapy to methyldopa prior to conception, especially if they require more

than one drug and it is unlikely that they will be able to discontinue therapy in early pregnancy. Labetalol, a combined alpha-blocker and beta-blocker, is an alternative to methyldopa, as it is well-tolerated with an easier twice-a-day dosing schedule than methyldopa,[27]particularly for severe hypertension.

Beta-blockers is generally safe, but intrauterine growth retardation and pre-term birth have been reported.[28] Calcium channel blockers (CCBs) such as nifedipine are frequently used because of their use in stopping premature labor. A randomized controlled trial conducted by Webster L demonstrated that nifedipine controlled BP of chronic hypertension in pregnancy and reduced the incidence of severe hypertension without an increase in adverse perinatal outcome.[29] The use of sublingual nifedipine, however, should be avoided to minimize the risk of sudden maternal hypotension and fetal distress, caused by placental hypoperfusion. Amlodipine has been used in pregnancy but safety data are lacking.

There is increasing debate regarding discouraging the use of diuretics. The European Society of Hypertension/European Cardiology Society (ESH/ECS) 2013 guidelines state that the use of diuretics in pregnancy should be considered a possible or relative contraindication, while the British Hypertension Society (BHS) deemed the use of diuretics as a controversial issue associated with potential harmful effects on maternal and fetal outcomes. There could also be an increased risk of congenital abnormalities and neonatal complications if chlorothiazide is taken.

Table No. 4.

Variable	Recommendation	Controversy
Medications	Methyldopa or labetalol	Diuretics
	Avoid ACE inhibitors	
Blood-pressure goals	Women with mild-moderate hypertension and a normal BMI may choose to discontinue the use or reduce the doses of antihypertensive agents.	Specific blood-pressure levels for treatment and goal
Evaluation before pregnancy	Evaluate for secondary causesin presence of suggestivesymptoms or signs. In women with a history ofhypertension for severalyears, evaluate for target-organdamage, includingleft ventricular hypertrophy, retinopathy.	
Supplementations		Calcium, antioxidants, low-dose aspirin (60 mg daily)
Lifestyle	Healthy body weight. Adequate sodium and potassium intake.	The dose of sodium or potassium intake

ACE denotes angiotensin-converting enzyme, BMI body mass index.

5. Education

The most difficult problem for the management of pre-pregnancy hypertension was that the majority of women with chronic hypertension who became pregnant did not know their blood pressure and did not start hypertension management before pregnancy or when they are planning to become pregnant. Undiagnosed hypertensive women may appear normotensive in early pregnancy because of the normal fall in blood pressure, commencing in the first trimester. This may mask pre-existing hypertension, and when blood pressure is recorded later in the pregnancy it may be interpreted as gestational hypertension.

Since nearly 50% of pregnancies in USA are unplanned, it is very important to counsel women of reproductive age regarding both the importance of the blood pressure control and the adverse effects of the antihypertensive agents. Those with high blood pressure should be screened for underlying secondary causes and endocrine causes such as hyperaldosteronism.[30] This recommendation is enhanced by the Canadian.[34] Australasian and the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC) eight evidence guidelines for the management of high blood pressure in adults [l35], reinforcing the importance of looking for signs and symptoms of secondary hypertension in women with chronic hypertension who seek preconception counseling. Particularly, the presence of resistant hypertension, hypokalaemia (potassium levels <3.0 mEq/l), elevated serum creatinine level (>1.1 mg/dl) and family history of kidney disease are important suggestive findings of secondary hypertension.

In addition, age is the strongest risk factor for the occurrence of hypertension.[31] The prevalence of hypertension was 30% among adults over 18 years old in the USA, and in some other countries, as African American women have a higher prevalence of hypertension and at younger ages.[32,33] First birth rates for women 35–39 years old generally increased from the mid-1970s to 2012, while steady increases for women 40–44 years old began later in the 1980s, which may cause the increased risk of pregnancy-associated hypertension and related adverse delivery outcomes. Childbirth at earlier ages could bring much more benefits for decreasing the risk of delivery complications and improving childhood developmental outcomes.

6. Women with long-term hypertension

Long-term hypertension induces damage to the vasculature,[34] myocardium, kidney[35] and other organs.[36] Thus, before pregnancy,women with long-term hypertension (usually more

than 4 years), are recommended to undergo assessment of left ventricular function with echocardiography or electrocardiography,[17] according the guidelines from ACOG, 2013. Additionally, if the urinalysis is positive for protein, then a 24-h urine collection for protein analysis or measurement of spot urine protein-to-creatinine ratio should be assessed.[37,38] For those with target organ damage, contraception (the Copper T380A) is important for helping them achieve optimal timing of pregnancy in relation to the optimal control of their condition.[39]

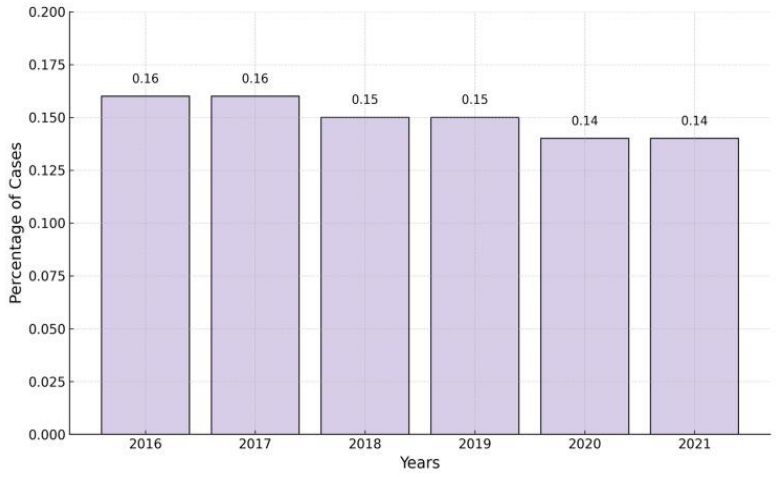

Figure No. 1: Hansika Venkatesan: Global percentage incidence of maternal hypertension disorders among females aged 20+ years from 2016 to 2021.

7. FUTURE PERSPECTIVE

It is clear that further research is required to determine optimal antihypertensive choice in pregnancy. This has been highlighted in the 2020 James Lind Alliance Priority Setting Partnership pregnancy hypertension top 10 research priorities.[40] and research recommendations from the 2019 update of the UK NICE Hypertension in Pregnancy Guidelines.[61] both of which highlighted the need to define optimal antenatal antihypertensive medication (clinical effectiveness and safety from a maternal and infant perspective) in pregnancy. These questions are being addressed by the Giant PANDA trial, which is randomizing 2300 women to nifedipine versus labetalol and has a co-primary maternal superiority outcome (proportion of BP readings with severe hypertension), and co-primary non-inferiority neonatal outcome (fetal loss, neonatal death or neonatal unit admission). The trial, due to be completed in 2025, will provide high-quality evidence that will inform national and international clinical practice guidelines. However, the challenge of answering this research question was highlighted in the 2022 network meta-analysis of

antihypertensives for treatment of mild-to-moderate hypertension. Sample size calculations comparing antihypertensive agents powered on reduction in maternal severe hypertension suggested 2500–10,000 participants/group are necessary to detect a 20% reduction, with prohibitive sample sizes for neonatal outcomes.[62] Therefore further meta-analyses and use of observational and electronic health record data may be required to further delineate antihypertensive maternal and fetal/neonatal risk-benefit profiles.

The latest version of the ISSHP guidelines (2021).[63] included one research recommendation pertaining to antihypertensives: whether hemodynamic-guided antihypertensive therapy can achieve maternal BP control and optimize perinatal outcomes. This reflects the growing interest in personalization of antihypertensive agent treatment in pregnancy, a compelling concept given the relatively short time frame of pregnancy and potential for good BP control to improve maternal and infant outcomes including reduction in pre-eclampsia.[64] Practising obstetricians will be familiar with the experience that some women respond better to labetalol/beta-blockers better than nifedipine/calcium channel blockers or vice versa. While several theories exist as to what may be driving treatment response in pregnancy and variation in clinician prescribing is observed,[65] the evidence base is not yet sufficiently robust to have translated into clinical guidelines.

Several factors have been put forward as potential guides of antihypertensive agent in choice in pregnancy including maternal hemodynamics, maternal ethnicity and a growing interest in pharmacogenomics. Maternal hemodynamic profiles have been best characterized in pre-eclampsia, with early-onset pre-eclampsia demonstrating a vasoconstricted, low cardiac output profile (‘hypodynamic’), and late-onset pre-eclampsia typically characterized by a high cardiac output, lower systemic vascular resistance profile (‘hyperdynamic’) [66],[41] It is biologically plausible that beta-blockers may be more effective in individuals with hyperdynamic profiles, while calcium channel blockers and methyldopa may be more effective in those with hypodynamic profiles, as highlighted in a recent European Society of Hypertension position statement on management of HDP [42] This has been suggested by two small studies investigating hemodynamic-driven prescribing.[44],[45] These studies show promise but require validation, with further small studies ongoing (NCT04755764). It is possible that normalizing maternal hemodynamics as an adjunct goal of antihypertensive agent therapy may improve maternal and fetal outcomes.[43] In addition, studies have demonstrated women with vasoconstricted profiles have the highest rates of fetal growth

restriction warranting additional study of how to optimize fetal outcomes in this high-risk group.[44],[45] However, robust reproducible measures of maternal hemodynamics remain challenging.[66] Further studies investigating maternal biomarkers such as placental growth factor (PlGF), hemodynamics and response to antihypertensive agents may pave the way for future stratified trial designs.

UK NICE guidelines recommend tailoring of antihypertensive treatment for chronic hypertension in non-pregnant adults on the basis of ethnicity and age (NG136, updated 2019) [67] on the premise that there is a higher prevalence of low-renin hypertension in individuals of African ancestry,[46],[47] leading to an attenuated response to beta-blockers and angiotensin converting enzyme inhibitors (which work primarily by suppressing the renin-angiotensin system), and better response to calcium channel blockers (which work primarily by vasodilation). While little data exist in pregnancy, small studies suggest similar patterns may be observed in pregnancy. In a study of 117 pregnant women with treated chronic hypertension, women classified as being of Black ethnicity had lower renin and aldosterone concentrations across gestation.[48] Furthermore, in a study of 120 pregnant hypertensive women prescribed labetalol monotherapy, BP control (defined as BP < 140/90 mmHg) was almost 20% lower in women of Black versus White ethnic backgrounds.[49] Maternal ethnicity has also been shown to be an independent predictor of labetalol response alongside baseline heart rate and stroke volume index.[50]

However, ethnicity is a complex and controversial concept which may encompass primarily social as opposed to biological features.[51],[52] Future studies should aim to disentangle whether maternal ethnicity is acting as a proxy for primarily social or genetic variation in this context, with genetic ancestry being one potential route of exploration to elucidate biological determinants.[53],[54] In parallel, research and actions to address equity of access to and quality of care across women of all ethnicities and deprivation indices, particularly for women facing multiple disadvantage, are crucial to tackle social determinants of adverse outcomes.[55]

Pharmacogenomics is also gaining interest as a precision medicine approach in pre-eclampsia and HDP[56],[57] Studies to date have primarily focused on variants associated with response to any antihypertensive in pre-eclampsia, finding variants in MMP9, TIMP1 and NAMPT are associated with response.[56],[57] Only one study has investigated drug-specific response, suggesting variants in the cytochrome P450 CYP2D6 gene (rs1065852) may be associated

with efficacy of labetalol treatment.[58] However, studies to date are small and consensus on definition of treatment response is required to progress research in the field.[56]

Alongside a better evidence base to inform and personalize antihypertensive agent selection, BP treatment thresholds and targets may continue to evolve in line with out-of-pregnancy hypertension management [Citation28]. Two small trials are currently investigating whether treatment of Stage 1 hypertension (BP 120–139/80-89 mmHg) in early pregnancy (<20 weeks) improves maternal and fetal outcomes (NCT05955040, NCT05989581).

Finally, further research into the pathophysiology of HDP is required to yield targeted treatments for prevention and management of HDP beyond the current options of control of BP and delivery of the fetus and placenta. Notably, small inhibitory RNA (siRNA) based technology is being investigated as a potential therapeutic agent to silence placental expression of placental soluble fms-like tyrosine kinase 1 (sFLT1), a validated diagnostic and prognostic marker which is over-expressed in pre-eclampsia.[59] Large-scale multi-omic studies are also starting to identify the biological pathways in HDP and may lead to further development of targeted therapies for pre-eclampsia and HDP.[60]

7. VIEWPOINT: management of hypertension in pregnancy in 2035

We anticipate that in 10 years' time, optimal BP treatment thresholds and targets will have been defined, accepted into clinical practice and used internationally. We speculate that high-quality trial and observational data will have generated a solid evidence base to inform antihypertensive agent selection and counseling in pregnancy. Furthermore, point-of-care measurements or tests, which could include maternal hemodynamics, pharmacogenomics or blood tests (e.g. PlGF, s-Flt) may be used alongside appropriate monitoring such as 24-hour ambulatory BP monitoring or remote BP monitoring to rapidly select and titrate antihypertensives in pregnancy. Novel, targeted therapeutics may also be emerging to modify the course of hypertensive disease in pregnancy.

8. CONCLUSION

In summary, managing hypertension in pregnancy requires careful selection of safe antihypertensives to minimize maternal and fetal risks. Beta-blockers like labetalol and methyldopa remain first-line for chronic and gestational cases, while avoiding RAAS inhibitors is critical. Guidelines emphasize pre-conception planning, regular monitoring, and

multidisciplinary care for preeclampsia. Future research should focus on pre-pregnancy strategies and long-term outcomes to optimize treatments.

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