Seminars in Perinatology 38 (2014) 487–495

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/semperi

Pharmacological management of hypertension in pregnancy

Thomas R. Easterling, MD

Department of Obstetrics and Gynecology, University of Washington, Seattle, WA 98195

ARTICLE INFO

Keywords:
pregnancy
hypertension
preeclampsia
IUGR
antihypertensive

ABSTRACT

Hypertension in pregnancy remains a significant public health problem. Pharmacological management of blood pressure in pregnancy is impacted by changes in maternal drug disposition and by the pharmacodynamic effects of specific agents. This article will review the impact of pregnancy on pathways of drug elimination and the associated clinical implications, the pharmacodynamic effects of specific drugs and classes of drugs in pregnancy, and the data to date on the impact of antihypertensive therapy on mothers and their fetuses.

Introduction

Hypertension in pregnancy remains a significant public health problem. Preeclampsia, chronic hypertension, and severe gestational hypertension, while subject to different diagnostic criteria, contribute to maternal and perinatal morbidity and mortality. Hypertensive pregnant women are at risk for cerebrovascular accident, cerebral edema, hepatic rupture, renal failure, heart failure, and death. Hypertension diagnosed in pregnancy identifies women at risk for subsequent cardiovascular disease when not pregnant. The fetuses of hypertensive women are at risk for complications of preterm birth after delivery for maternal indications, intrauterine growth restriction, and stillbirth. The risk for the severest of outcomes such as maternal mortality and cerebral injury is moderated through prenatal care. Indicated early delivery protects the mother and the neonate from stillbirth —often at the cost of preterm delivery and its associated complications.

A number of "single-molecule adjunctive therapies" have been suggested for the prevention of preeclampsia with the potential for improving maternal and perinatal outcomes. Large trials of treatment of high- and low-risk women with aspirin, calcium, and antioxidants have not supported benefit. Meta-analyses, including smaller trials with greater variability, have continued to support some potential benefit for aspirin—but with relatively limited impact.

Outside pregnancy, hypertension is clearly associated with adverse outcomes, and treatment has been demonstrated to improve outcomes. Treatment of hypertension in pregnancy remains controversial in part due to assumptions that high blood pressure itself is not "in the pathway" of adverse outcomes. Some advocate only treating severe hypertension (>160/110 mmHg) and then treating aggressively with parenteral medications. In the absence of conflicting data, others argue that pregnant women should be treated as one would a woman who is not pregnant. Given the severity of associated maternal complications and the short time frame of disease progression, others argue that women at high risk for adverse outcomes should be treated aggressively by high-risk JNC-7 standards.[1] Each of these positions seeks to balance the risk of adverse maternal outcome and of preterm delivery against

The described work was supported by National Institutes of Health Eunice Kennedy Shriver National Institute of Child Health and Human Development, USA (Grant no. U10-HD047892) (in support of the Obstetric–Fetal Pharmacology Research Unit Network).

E-mail address: easter@u.washington.edu

http://dx.doi.org/10.1053/j.semperi.2014.08.016
0146-0005/

the potential risk of treatment to the fetus—in particular the impact on fetal growth. Statements of opinion have been published with acknowledgment that clear supporting data is lacking. Recommendations and opinions remain controversial. Having said that, the failure to adequately treat hypertension has been cited by the Joint Commission[2] as a major cause of preventable maternal mortality in the United States.

The American College of Obstetricians and Gynecologists has recently completed a review of the management of hypertension in pregnancy by a task force of experts in the field.[3] The task force was able to make six recommendations where the quality of evidence was "High" and the recommendation was "Strong." Of five recommendations pertaining to pharmacological management, two supported the use of antenatal steroids in hypertensive women to improve pulmonary function in babies born prematurely. Two supported the use of magnesium sulfate in women with severe hypertension. One recommended against the use of antioxidant supplementation with vitamins C and E. An additional 19 recommendations were made where the quality of evidence was "Moderate" and the strength of recommendation was "Strong." Eight of the 19 pertained to pharmacological management. Two supported the use of antenatal steroids and two supported the use of magnesium sulfate. Two recommended that systolic blood pressure $\geq$160 mmHg and diastolic blood pressure $\geq$105 mmHg should be treated. One recommended labetalol, nifedipine, and methyldopa for initial management of hypertension in pregnancy. One recommendation cautioned against the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, and mineralocorticoid receptor antagonists in pregnancy. An additional 31 recommendations were made where the quality of evidence was "Low" to "Moderate" and the strength of recommendation was "Qualified." The report of the Task Force on Hypertension in Pregnancy highlights the need for research in the field: "… there are few recommendations that can be classified as "strong" because there are huge gaps in the evidence that guides therapy. These knowledge gaps form the basis for future research recommendations to guide therapy."[3]

A variety of antihypertensive medications have been used in pregnancy. Table 1 lists those commonly used and summarizes their pathways of drug disposition, the impact of pregnancy on these pathways when known, the primary mechanism of action, and the primary and secondary hemodynamic changes. This article will review the pharmacokinetics and pharmacodynamics of antihypertensive drugs in pregnancy and then briefly summarize information to date on efficacy.

Pharmacokinetics of antihypertensive agents in pregnancy

Physiological adaptations to pregnancy directly impact drug disposition. Increased cardiac output in pregnancy is associated with increased renal blood flow and hepatic blood flow. Increased renal blood flow directly increases glomerular filtration and the clearance of many drugs. Increased activity of renal tubular transporters such as p-glycoprotein and organic ion transporters will increase renal secretion clearance in excess of that due to increased GFR alone. When present in the placenta, transporters may limit transport to the fetus. Increased hepatic blood flow will increase the first-pass metabolic clearance of drugs with high extraction ratios. Induction of cytochrome p-450 enzymes (CYP3A and CYP2D6) and conjugation activity will increase metabolic clearance of other drugs.

Table 1 – Commonly used antihypertensive agents in pregnancy.

Drugs by class	Disposition	Impact of pregnancy on disposition	Mechanism of action	Hemodynamic effect
β-Blockers			↓Heart rate	↓HR ↓CO
Atenolol	Renal	↑		↑TPR ↑SV
Metoprolol	CYP2D6	↑↑↑		
Propranolol	CYP2D6	↑↑↑		
Mixed effect				↓TPR
Labetolol	Conjugation to glucuronide	↑↑↑β-Isomer ↑α-Isomer	↓Vascular resistance ↓HR (at higher doses)	→HR→CO
Central α-agonists			↓Central adrenergic output	↓TPR
Methyldopa	Renal, conjugation	?		↓HR ↓CO
Clonidine	Renal	↑		*Individual variability*
	CYP-2D6	↑↑↑		
Vasodilators			↓Vascular resistance	↓TPR
Ca channel blockers				↑↑HR ↑CO
Nifedipine	CYP3A	↑↑		
Amlodipine	CYP3A	↑↑		
Hydralazine	Acetylation	?		
Diuretics			↓Vascular volume	↓SV ↓CO
Furosemide	Conjugation to glucuronide	?		↑TPR ↑HR

TPR—total peripheral resistance; HR—heart rate; CO—cardiac output; SV—stroke volume; ?—unknown; ↑—increased; ↓—decreased; →—no change.