Antihypertensive Therapy in Pregnancy

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Current Hypertension Reports 2001, 3:392–399
Current Science Inc. ISSN 1522-6417
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Human pregnancy, normally characterized by systemic vasodilation and modest hypotension, can be complicated by underlying maternal hypertension and several unique hypertensive disorders, including pre-eclampsia. Although well-designed and adequately powered clinical trials are critically needed, there have been several recent meta-analyses of this large literature, along with consensus statements and treatment guidelines from three distinct multidisciplinary groups of clinicians and investigators. In this paper we review recent analyses and guidelines, advising on our current approach to antihypertensive therapy in pregnant women.

Introduction
Hypertension in pregnancy remains a major cause of morbidity and mortality in the mother and fetus in both western and developing nations. Much of this morbidity occurs in women with chronic hypertension, especially in those who develop superimposed pre-eclampsia. In 1976 Redman et al. [1] published a landmark report describing their randomized trial of methyldopa to treat chronic hypertension in pregnant women. There have been other trials since then, some of excellent quality, and considerable progress has been made towards understanding the etiology and pathophysiology of the hypertensive disorders complicating gestation, particularly pre-eclampsia [2••]. Yet, as we start this millennium, there are few guidelines on how to manage the most challenging of pregnant patients, the gravida with pre-existing essential hypertension, including when and how to treat with antihypertensive drugs. In the following sections we review evidence guiding antihypertensive therapy in pregnant women; assess the contributions of studies that shed light on the mechanisms of hypertension in gravidas; direct the reader to several recent and ongoing efforts that use the tools of meta-analysis to provide a structured review of this inadequate literature; highlight specific treatment recommendations of the expert panels that have recently opined on this subject [3••–5••]; and present recommendations for critically needed research in the area. Not discussed here are current recommendations for clinical surveillance of hypertensive gravidas, treatment of eclamptic seizures, risk factors for pre-eclampsia or strategies for its prevention, or guidelines for counseling these patients; these have all been recently reviewed elsewhere [2••,6,7].

Maternal and Fetal Risks of Hypertension in Pregnancy
Regarding risk, we first must ask the following: 1) what are the short-term risks of hypertension during pregnancy, 2) do available treatment trials allow us to advocate antihypertensive use for their control, 3) can we adequately assess the comparative safety and efficacy of available antihypertensives, and 4) can we define appropriate therapeutic goals and treatment protocols?

The major maternal risk associated with underlying hypertension that might justify pharmacotherapy is superimposed pre-eclampsia, whose complications account for most, but not all, of the morbidity ascribed to chronic hypertension during pregnancy [8]. Other risks that could conceivably be modified by treatment include placental abruption, accelerated hypertension leading to hospitalization or to target organ damage, and cerebral vascular catastrophes [9]. It is also conceivable that treatment might avert the fetal risks that include death, growth retardation, neonatal morbidity, and early delivery, the latter occurring in many cases due to concerns regarding maternal safety. Unfortunately, we have little data to support most of the above assumptions, and we need unequivocal answers to these questions for the following reasons: First, although the diagnosis of superimposed pre-eclampsia is often difficult in the setting of chronic hypertension (the careful clinician should always err in favor of cautious overdiagnosis), several well-conducted studies suggest that superimposed pre-eclampsia will complicate at least 15% to 20% of pregnancies in women with blood pressures greater than 140/90 mm Hg, with increased risk at higher values [9,10]. Second, hypertension doubles the incidence of placental abruption [9,11•], and in one large prospective study the risk was further increased threefold when chronic hypertension was complicated by superimposed pre-eclampsia [9]. Finally, chronic hypertension is associated, with remarkable consistency, with a threefold increase in perinatal mortality [11•], along with impaired fetal growth and neonatal outcome; early delivery, perinatal
death, and neonatal complications are even more frequent in women with either superimposed pre-eclampsia or with target organ damage as evidenced by proteinuria at baseline [9].

Currently, it appears that treatment of underlying hypertension does not prevent superimposed pre-eclampsia, abruptio placenta, or reliably decrease perinatal mortality; however, these conclusions are based on the results of several small trials whose results vary considerably [11–14•]. The major apparent benefit of antihypertensive therapy appears to be decreased occurrence of severe hypertension and hypertension necessitating hospital admission later in pregnancy [12•–14•]. This more limited outcome remains clinically important since blood pressures as low as 170/110 mm Hg are clearly associated with cerebrovascular hemorrhage in pregnant women, leading experienced clinicians to treat such values as a medical emergency; improved blood pressure control also provides the reassurance required to permit safer prolongation of the pregnancy, with its attendant benefit to the neonate. Importantly, since the relative risks of “hard” morbid endpoints are low in mild hypertension, and none of the available trials are either comprehensive or adequately powered, our ability to advocate specific guidelines depends more on considerable clinical experience [3••–5••] in combination with a critical evaluation of an unfortunately inadequate literature [2••,6,11•–16•], than on clear data.

Enthusiasm for aggressive control of underlying mild hypertension is further tempered by relatively unknown fetal and remote childhood risks of antihypertensive drug exposure in utero. In this respect, while several recent small studies have assessed some measures of fetal and neonatal growth, development, and function [17–19], the continued preference of many workers for methyldopa as the first-line agent for blood pressure control in pregnancy relates to its apparent safety, demonstrated, albeit in small numbers, through 7.5 years follow-up of children exposed in utero [20].

The Australasian Society for the Study of Hypertension in Pregnancy has advocated drug therapy to maintain maternal pressures of less than 140/90 mm Hg [4••], a goal shared by the Canadian Hypertension Society for some groups of women at perceived excess risk [5••]. We prefer the recommendations of the National High Blood Pressure Education Program (NHBPEP) Working Group on Hypertension in Pregnancy [3••], with somewhat higher threshold pressures for (re)instituting treatment (150–160/100–110 mm Hg), and somewhat less stringent targets for blood pressure control (but would treat at lower levels in select patients, such as those with underlying renal disease). This preference is in accord with a recent meta-regression analysis of results from 14 trials that suggested that tighter control of maternal mean arterial pressure might contribute to fetal growth restriction, irrespective of the specific agents used [21]. This conclusion gains physiologic plausibility from the presumed inability of intervillous placental blood flow to autoregulate with reduced perfusion pressure. However, despite the accord between this metaregression analysis and the NHBPEP Working Group guidelines, we believe that a definitive prospective trial specifically focused on the maternal and fetal effects of differing levels of targeted (and achieved) blood pressure control has yet to be performed and is critically needed.

Maternal Hemodynamics During Normal and Hypertensive Pregnancy
Normal pregnancy is marked by early systemic vasodilation; decrements in systemic vascular resistance are so large that mean arterial pressure falls by approximately 10 mm Hg despite 40% to 50% increases in blood volume and cardiac output [2••]. Blood pressure is maximally decreased by midpregnancy, increasing gradually towards term. Women with underlying essential hypertension may exhibit an even greater early gestational fall in blood pressure, by as much as 15 to 20 mm Hg [2••,22], so as to either obscure recognition of their underlying condition or to make continued treatment unnecessary.

The hypertension in pre-eclampsia is characterized by primary intense systemic vasoconstriction, as determined by invasive hemodynamic measurements [2••,23]. The vasoconstriction is associated with modest decrements of cardiac output, but with normal left ventricular filling pressures. Curiously, there is now evidence that some women destined to develop pre-eclampsia exhibit even greater than normal increments in cardiac output prior to the onset of hypertension, their cardiac outputs falling with onset of the systemic vasoconstriction and hypertension that characterize overt disease [24]. Women who develop (nonproteinuric) gestational hypertension share this early exaggerated increase in cardiac output but maintain their hyperdynamic circulation, with low peripheral resistance, throughout pregnancy. Easterling et al. [25] hypothesized that treatment of this early excessive cardiac output with atenolol would prevent subsequent pre-eclampsia; this prediction was supported by a pilot study of 56 hemodynamically selected and initially normotensive gravidas [25]. However intriguing, this preliminary report neither offers guidance on the treatment of already hypertensive women, nor allows us to balance the fetal risks of more widespread β-blocker use against possible maternal benefit. Pre-eclampsia is further characterized by markedly increased sympathetic outflow [26], which, although not a likely cause of the hypertension, has been taken by many as a mechanistic justification for the initial selection of agents such as methyldopa.

The renin-angiotensin system is activated in normal human pregnancy [27]. Even in pre-eclampsia, where angiotensin II levels are lower than in normal gestation, there may be simultaneous upregulation of AT1 receptors, accompanied by mechanistically fascinating evidence for the production of AT1 receptor agonistic autoantibodies [28]. Thus, angiotensin converting enzyme (ACE)