TREATMENT OF HYPERTENSION IN PREGNANCY

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ABSTRACT

In pregnancy, there is general agreement that severe hypertension should be treated with antihypertensive agents. There is no agreement as to whether mild-moderate elevations of blood pressure should be so treated. If antihypertensive agents are used, there are a large number of choices, and selection may be influenced by the stage of pregnancy and the severity of hypertension.

Key Words: hypertension, antihypertensives, pregnancy, complications

Hypertensive disorders complicate 5-10% of pregnancies and are a leading cause of maternal mortality in both the developed and developing world. Hypertension in pregnancy is defined as diastolic blood pressure (dBP) >90mmHg.[2] Although 24-hour ambulatory and home self-measurement of blood pressure (BP) are gaining popularity, the standard of care is still (preferentially serial) office BP measurements.

The term 'hypertensive disorders of pregnancy' (HDP) is used to reflect the fact that we are dealing with more than elevated blood pressure. Gestational hypertension with proteinuria and/or adverse features[2], also known as 'pre-eclampsia', is a disorder that originates with uteroplacental mismatch, with subsequent diffuse maternal endothelial cell dysfunction and maternal (+/- fetal) end-organ complications. It follows therefore, that management of HDP has many aspects that cannot be addressed here, including reducing the risk of 'pre-eclampsia' in women at increased risk by use of low-dose aspirin[3] and potentially antioxidant therapy [INTAPP (International Trial of Antioxidant Prophylaxis in Pregnancy)],[4] monitoring of maternal and fetal well-being; ruling out other secondary causes of hypertension; timing and method of delivery; use of MgSO4 for prophylaxis against and treatment of eclampsia,[5,6] and counseling about the long-term increased risk of hypertension and with 'pre-eclampsia' in particular, cardiovascular morbidity and mortality.[7]

At gestational ages remote from term, antihypertensive therapy is used to protect maternal well-being while prolonging pregnancy in the hopes of minimizing complications related to iatrogenic prematurity. Postpartum, antihypertensive therapy is used while allowing resolution of pregnancy-related changes.

There is general agreement that severe hypertension, conventionally defined as a BP >170/110mmHg, should be treated to avoid severe maternal, particularly cerebrovascular, complications.[8-10] The most frequently prescribed short-acting antihypertensive agents are hydralazine, labetalol, and according to a national Canadian survey, MgSO4.[11] The objective of such treatment is to lower acutely elevated mean arterial BP by approximately 25%, over hours, without causing maternal hypotension or a non-reassuring fetal heart rate tracing that would precipitate Caesarean section.

It is unclear which agent is best to achieve these goals,[12] with some evidence pointing towards an excess of maternal hypotension and Caesarean section with hydralazine compared with other antihypertensives, most commonly labetalol or calcium channel blockers.[13] There is also controversy over whether use of short-acting nifedipine should be relatively contraindicated in women who are on MgSO4, due to concerns

about maternal neuromuscular blockade.[8,14,15] It should be emphasized that women with pre-eclampsia are intravascular volume depleted, even when very edematous, and maternal hypotension is a risk when administering any short-acting antihypertensive.

There is no agreement about whether or not mild to moderate pregnancy hypertension, conventionally defined as dBP of 90-109mmHg, should be treated with antihypertensive therapy for either maternal or fetal reasons. Canadian(10) and Australian[9] guidelines recommend treating dBP values between 90-95mmHg (particularly when gestational age is <28 weeks, and/or there is gestational hypertension with proteinuria), whereas American guidelines advise treatment for dBP >105mmHg[8] There is currently a Canadian-led trial, CHIPS (Control of Hypertension In Pregnancy Study), that is designed to determine whether, for women with non-proteinuric hypertension at <34 weeks, 'less tight' control (aiming for a dBP of 100mmHg) or 'tight' control (aiming for a dBP of 85mmHg) is better for baby without increasing maternal risk.[16]

Women who have target-organ damage, renal disease or pre-gestational diabetes, should have their BP normalised during pregnancy, as in non-pregnancy, even over months. Whether or not the same BP goal (<130/80mmHg or <125/75mmHg in the presence of >1g/d of proteinuria) should be chosen in pregnancy has not been studied, and the impact on intrauterine fetal growth remains uncertain.

There are many agents available for the treatment of mild to moderate hypertension in pregnancy. Canadian practitioners report the most frequent use of methyldopa and labetalol[11], a practice that is consistent with national and international guidelines.[8-10]

Although no antihypertensive has been found to be teratogenic, ACE inhibitors and angiotensin-receptor blockers are contraindicated for use in later pregnancy because of fetotoxicity (i.e., oligohydramnios or perinatal renal failure). Although beta-blockers have been identified as causing intrauterine growth restriction[17], this would appear to be a risk with any antihypertensive therapy, in proportion to the fall in mean arterial pressure.[18, 19] The risk with beta-blockers is no greater than it is with other antihypertensives, including methyldopa.[17]

For reasons that are not clear, one possible exception to this assessment of risk may be atenolol, particularly when used in early pregnancy.[20] Given that there are so many agents available for use in pregnancy, atenolol may be best avoided until definitive data become available.

It is unclear what proportion of women with hypertension during pregnancy will develop hypertension postpartum, however, the risk seems to be greatest in women with severe pre-eclampsia.[21] Women may also develop de novo postpartum hypertension, particularly on days 3-6 postpartum when all women have the highest BP; this is probably due to mobilization into the intravascular space of salt and water accumulated throughout pregnancy. Whether or not to consider postnatal antihypertensive therapy is unclear and remains a personal decision given the lack of adequate evidence.[22]

No antihypertensive agent is contraindicated for use during breastfeeding, and all have been shown to, or are thought likely to, cross into breast milk in variable quantities. The amount received by a breastfeeding infant is probably very small, and commonly used antenatal antihypertensives, as well as ACE inhibitors, are considered to be compatible with breastfeeding[23] Good choices among antihypertensive agents are those with high-protein binding and low lipid solubility, such as labetalol and captopril.

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REFERENCES

1. Why mothers die 1997-1999. The confidential enquiries into maternal deaths in the UK. London: RCOG Press, 2001.
2. Helewa ME, Burrows RF, Smith J, Williams K, Brain P, Rabkin SW. Report of the Canadian Hypertension Society Consensus Conference: 1. Definitions, evaluation and classification of hypertensive disorders in pregnancy. CMAJ 1997; 157(6):715-725.

3. Duley L, Henderson-Smart D, Knight M, King J. Antiplatelet drugs for prevention of pre-eclampsia and its consequences: systematic review. British Medical Journal 2001; 322(7282):329-333.
4. INTAPP (INternational Trial of Antioxidant Prophylaxis in Pregnancy). Lise Tremblay@justine umontreal ca 2003.
5. Duley L, Farrell B, Spark P, Roberts B, Watkins K, Bricker L et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet 2002; 359(9321):1877-1890.
6. Duley L, Carroli G, Belizan J, Gonzalez L, Campodonico L, Bergel E et al. Which Anticonvulsant for Women with Eclampsia - Evidence from the Collaborative Eclampsia Trial. Lancet 1995; 345(8963):1455-1463.
7. Irgens H.U., Reisaeter L., Irgens L.M., Lie R.T. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. BMJ 2001; 323:1213-1217.
8. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000; 183(1):S1-S22.
9. Brown MA, Hague WM, Higgins J, Lowe S, McCowan L, Oats J et al. The detection, investigation and management of hypertension in pregnancy: executive summary. Aust N Z J Obstet Gynaecol 2000; 40(2):133-138.
10. Rey E, LeLorier J, Burgess E, Lange IR, Leduc L. Report of the Canadian Hypertension Society Consensus Conference: 3. Pharmacologic treatment of hypertensive disorders in pregnancy. CMAJ 1997; 157(9):1245-1254.
11. Caetano M, Ornstein M, von Dadelszen P, Hannah ME, Logan AG, Gruslin A et al. A survey of Canadian practitioners regarding the management of the hypertensive disorders of pregnancy. Hypertens Pregn. In press.
12. Duley L, Henderson-Smart DJ. Drugs for rapid treatment of very high blood pressure during pregnancy. Cochrane Database Syst Rev 2000;(2):CD001449.
13. Cham C., von Dadelszen P, Waterman EJ, Magee LA. Is hydralazine the drug of choice for treatment of severe hypertension in pregnancy? A meta-analysis of clinical trials. BMJ. In press.
14. Ben Ami M, Giladi Y, Shalev E. The combination of magnesium sulphate and nifedipine: a cause of neuromuscular blockade. Br J Obstet Gynaecol 1994; 101(3):262-263.
15. Snyder SW, Cardwell MS. Neuromuscular Blockade with Magnesium-Sulfate and Nifedipine. American Journal of Obstetrics and Gynecology 1989; 161(1):35-36.
16. CHIPS (Control of Hypertension In Pregnancy Study): The Pilot Trial. www.utoronto.ca/miru/chips 2003.
17. Magee LA, Duley L. Oral beta-blockers for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev 2000;(4):CD002863.
18. von Dadelszen P, Magee LA. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: an updated metaregression analysis. JOGC 2002; 24:941-945.
19. von Dadelszen P, Ornstein MP, Bull SB, Logan AG, Koren G, Magee LA. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: a meta-analysis. Lancet 2000; 355(9198):87-92.
20. Bayliss H., Churchill D., Beevers M., Beevers D.G. Anti-hypertensive drugs in pregnancy and fetal growth: Evidence for "pharmacological programming" in the first trimester? Hypertens Pregn 2002; 21:161-174.
21. Tan LK, de Swiet M. The management of postpartum hypertension. Bjog-An International Journal of Obstetrics and Gynaecology 2002; 109(7):733-736.
22. Sadeghi S, Magee LA. Treatment for postpartum hypertension (Protocol for a Cochrane Review). The Cochrane Library 2003;(Issue 2).
23. Beardmore KS, Morris JM, Gallery EDM. Excretion of antihypertensive medication into human breast milk: A systematic review. Hypertension in Pregnancy 2002; 21(1):85-95.