

Collaborative Care for the Identification of Pregnant Women at High Risk for the Development of Hypertensive Disorders

Fabio Angeli^{1*}, Enrica Angeli², Cristina Poltronieri¹ and Paolo Verdecchia³

¹Section of Cardiology, AUSL 2 Umbria, Perugia, Italy

²Gynecology Consult Service, iChakra, Foligno, Italy

³Department of Internal Medicine, Hospital of Assisi, Assisi, Italy

Hypertension-related disorders are the most common medical problems encountered during pregnancy and complicating approximately 6-11% of all pregnancies [1-3].

Hypertensive disorders during pregnancy are commonly classified into four categories: a) chronic hypertension, b) preeclampsia-eclampsia, c) preeclampsia superimposed on chronic hypertension and d) gestational hypertension (transient hypertension of pregnancy, or chronic hypertension identified in the latter half of pregnancy). In particular, gestational hypertension is actually preferred over the older term of pregnancy-induced hypertension [4].

In 2008, the Society of Obstetricians and Gynecologists of Canada (SOGC) released revised guidelines [5] that simplified the classification of hypertension in pregnancy into 2 categories, 'preexisting' and 'gestational' with the option to add "with preeclampsia" to either category in the presence of additional maternal or fetal symptoms or signs.

The category "hypertensive disorders of pregnancy" is an important cause of perinatal morbidity and mortality [1-3] contributing to stillbirths and fetal complications including abruptio placentae, intrauterine growth restriction, premature delivery, and intrauterine fetal death [4]. In addition, they rank among the leading causes of maternal mortality, particularly when elevated blood pressure (BP) is due to preeclampsia, either alone or superimposed on chronic vascular disease [2].

In the last years epidemiological data identified several risk factors for development of hypertensive disorders in pregnancy, generally with relative risks of 1.5 to 9.7 in meta-analyses and systematic reviews [6].

A recent survey [7] on 2334 healthy nulliparous pregnant women participating in two population-based prospective cohort studies, analyzed the potential role of maternal demographics and clinical characteristics commonly recognized during pregnancy as predictors of gestational hypertension. Results showed that weight, systolic and diastolic BP obtained at the antenatal booking visit, may be suitable to stratify the risk of becoming hypertensive before 36 weeks of gestation.

In addition, presence of antiphospholipid antibodies, history of pre-eclampsia, pre-existing diabetes, multiple pregnancy, nulliparity, family history of pre-eclampsia and age ≥ 40 are commonly associated to an increased risk for the development of hypertensive disorders [6-8]. The risk of pre-eclampsia is also increased with pre-existing hypertension and renal disease, a pregnancy interval of ≥ 10 years, and confirmed proteinuria [6-8].

More recently, other markers have been investigated as potential predictors of hypertensive disorders during pregnancy [9-12]. They include laboratory markers (plasminogen activator inhibitor, placental growth factor, von Willerand factor, C-reactive protein and serum uric acid), provocative biophysical tests (angiotensin II challenge test, roll-over test, isometric exercise test), urinary proteomics, inherited thrombophilias (factor V Leiden mutation, prothrombin gene

mutation, protein C or S deficiency and antithrombin III deficiency), antiphospholipid antibodies and abnormal maternal serum markers (alpha fetoprotein, human chorionic gonadotrophin and plasma tumor necrosis factor alpha) [9-12].

Although several risk factors have been proposed as potential predictors of hypertensive disorders during pregnancy, early prediction of hypertensive disorders in healthy and initially normotensive pregnant women remains problematic. Indeed, preeclampsia and eclampsia are etiologically complex and heterogeneous conditions [4,13,14]. No guidelines exist for an appropriate and cost-effectiveness screening and early detection of hypertensive disorders in the community and there is no uniformity in referral thresholds and assessment procedures [6]. In addition, systematic reviews suggest that any single test may lack predictive value or practical utility to be applied at large [9-11].

There is a growing international concern that medical expertise is needed in the identification of pregnant women at increased risk of hypertensive disorders. In particular, the core of this concern are the issues of which healthcare providers will be most qualified to develop risk prediction models for hypertensive disorders.

In this context, some collaborative studies between gynaecologists, internists and cardiologists used the combinations of different tests to develop multivariable risk models for the prediction of hypertensive disorders during pregnancy [8,15-17]. The use of multiple markers in a screening approach may reflect different aspects of the hypertensive disease process and increases the specificity and sensitivity of the screening [17].

In particular, some studies analyzed the additive value of instrumental techniques (electrocardiography [ECG] and ambulatory BP monitoring [ABPM]) and their combinations with maternal factors and biochemical markers to refine risk stratification for hypertensive disorders in pregnancy [8,15-17].

The additive role of ABPM for the risk stratification of hypertensive disorders during pregnancy is based on the poor ability of casual BP measurements to detect the real BP load of pregnant women. BP falls early in pregnancy and is usually 10 mmHg below baseline in the second trimester [18]. The tendency of BP to decrease in early pregnancy may

*Corresponding author: Fabio Angeli, Section of Cardiology, AUSL 2 Umbria, Perugia, Italy, Tel: +39-0742-24553; Fax: +39-0742-352832; E-mail: fangeli@cardionet.it

Received December 23, 2011; Accepted January 07, 2012; Published January 09, 2012

Citation: Angeli F, Angeli E, Poltronieri C, Verdecchia P (2012) Collaborative Care for the Identification of Pregnant Women at High Risk for the Development of Hypertensive Disorders. Internal Med: Open Access 2:e105. doi:10.4172/2165-8048.1000e105

Copyright: © 2012 Angeli F, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

mask the real BP load of women with abnormal BP before pregnancy and reduce the clinical impact of prediction models for hypertensive disorders developed on the basis of office BP measurements.

Consequently, a relatively large proportion of pregnant women may have masked gestational hypertension, undetected by office BP measurements, but revealed by ambulatory BP [19].

In this context, specific BP index and circadian patterns has been proposed to detect subgroups of pregnant women at increasing risk of developing hypertensive disorders [20-22]. Hermida et al. [21] described various circadian patterns of ambulatory pulse pressure (PP) in a large prospective cohort study of pregnant women. A significantly higher 24-h mean PP was observed in the group of patients who developed both gestational hypertension and preeclampsia when compared to those who had uncomplicated pregnancies. This difference was even greater in the third trimester than the second trimester. In addition, pregnant women at increased risk of hypertension disorders tend to have higher night-time ambulatory BP than women without development of hypertension complications during pregnancy [22].

A recent prospective screening study in nulliparous healthy women with singleton pregnancies [15], evaluated the potential additive role of standard ECG in the identification of women at increased risk for hypertensive complications.

At the first antenatal visit, 12-lead ECG was recorded; ECG tracings were interpreted in a central laboratory and the following ECG parameters were analyzed: heart rate (HR), QRS duration, corrected QT interval, Cornell voltage, presence of ST-T abnormalities and left atrial (LA) abnormality. The criteria used for the diagnosis of P wave abnormality in lead V₁ were: (1) bi-peak interval in deeply notched P wave with (2) terminal forces equal to or more negative than -0.04 mm•sec, as obtained from the product of the depth of the terminal negative deflection and its duration (Figure 1).

The primary outcome of the study was the development of gestational hypertension, pre-eclampsia and eclampsia. The secondary

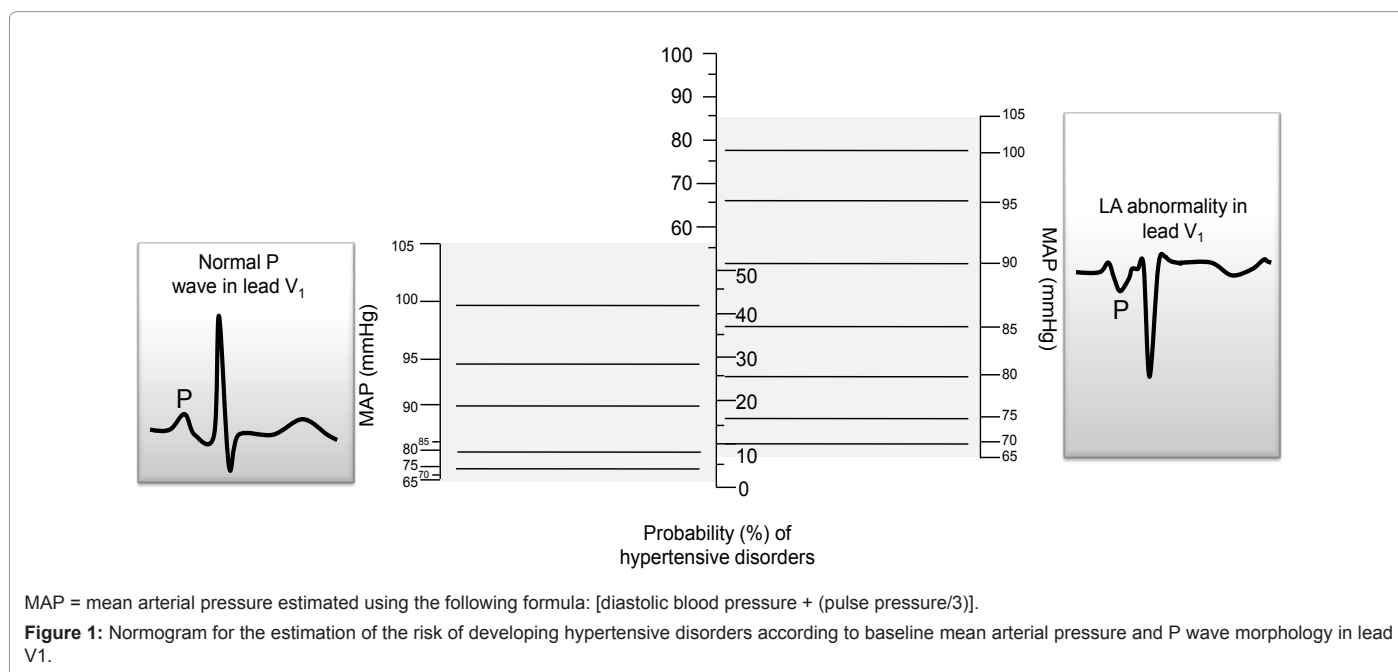
outcome was a composite measure of hypertensive disorders and other pregnancy complications including fetal growth restriction, HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, placental abruption, stillbirth, premature delivery and neonatal death.

Study population was sub-divided into two groups by occurrence of hypertensive disorders during pregnancy. At entry, women with development of hypertensive disorders differed under some aspects from those who did not experience these events: weight, body mass index (BMI) and BP were higher in women with hypertensive diseases than in those without (all $p < 0.05$). LA abnormality in lead V₁ was also more prevalent in women with hypertension disorders ($p=0.002$). Age, laboratory tests, HR and other ECG parameters did not differ between the two groups.

In a multivariable model, mean arterial pressure (MAP) and LA abnormality in lead V₁ were independent predictors of hypertensive disorders. In particular, the presence of LA abnormality in lead V₁ was associated to a 4-fold increased risk of developing hypertensive disorders (OR: 4.35; 95% confidence interval [CI]: 1.84-10.31; $p=0.001$).

The predictive model discriminated well between women who developed hypertensive disorders and women who remained normotensive during pregnancy, with an area under the curve (AUC) of 0.754 (95% CI: 0.667-0.841, $p<0.0001$). Although the primary outcome of the study was the development of hypertensive disorders, the same prediction model also proved significance to identify pregnant women at increased risk for the occurrence of maternal and fetal/neonatal complications.

A normogram to predict probability of hypertensive disorders and to facilitate the practical application of the model is depicted in the figure. As an example how to use this normogram, a woman with MAP of 80 mmHg at the booking visit and presence of LA abnormality in lead V₁ would have a probability of developing hypertensive disorders equal to 25%. In contrast, a woman with MAP of 80 mmHg and normal P wave in lead V₁ would have a probability of 7%.



Notably, abnormality of P-wave morphology in lead V₁ tested in this study as predictor of hypertensive disorders during pregnancy is commonly used as an ECG sign of LA enlargement and it may be easily diagnosed by traditional visual interpretation of ECG tracings, without any need of digitalization or other computer facilities [15].

In conclusion, most of the proposed risk markers used as screening test for the prediction of hypertensive disorders during pregnancy suffer from poor sensitivity and poor positive predictive values. However, the combinations of different tests and risk markers might improve the accuracy of multivariable predictive models for the prediction of hypertensive disorders of pregnancy, especially for the more severe forms. In this context, a collaborative care between different health providers may offer the opportunity to improve the ability in the identification of pregnant women at increased risk of hypertensive disorders.

Funding

This study was funded in part by the Fondazione Umbra Cuore e Ipertensione - ONLUS, Perugia, Italy.

Conflict of Interest

None of the authors of this study has financial or other reasons that could lead to a conflict of interest.

References

1. Berg CJ, Chang J, Callaghan WM, Whitehead SJ (2003) Pregnancy-related mortality in the United States, 1991-1997. *Obstet Gynecol* 101: 289-296.
2. Chang J, Elam-Evans LD, Berg CJ, Herndon J, Flowers L, et al. (2003) Pregnancy-related mortality surveillance--United States, 1991--1999. *MMWR Surveill Summ* 52: 1-8.
3. MacKay AP, Berg CJ, Duran C, Chang J, Rosenberg H (2005) An assessment of pregnancy-related mortality in the United States. *Paediatr Perinat Epidemiol* 19: 206-214.
4. (2000) Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol* 183: S1-S22.
5. Magee LA, Helewa M, Moutquin JM, von Dadelszen P (2008) Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *J Obstet Gynaecol Can* 30: S1-48.
6. Milne F, Redman C, Walker J, Baker P, Bradley J, et al. (2005) The pre-eclampsia community guideline (PRECOG): how to screen for and detect onset of pre-eclampsia in the community. *BMJ* 330: 576-580.
7. Nijdam ME, Janssen KJ, Moons KG, Grobbee DE, van der Post JA, et al. (2010) Prediction model for hypertension in pregnancy in nulliparous women using information obtained at the first antenatal visit. *J Hypertens* 28: 119-126.
8. Poon LC, Kametas NA, Maiz N, Akolekar R, Nicolaides KH (2009) First-trimester prediction of hypertensive disorders in pregnancy. *Hypertension* 53: 812-818.
9. Briceno-Perez C, Briceno-Sanabria L, Vigil-De Gracia P (2009) Prediction and prevention of preeclampsia. *Hypertens Pregnancy* 28: 138-155.
10. Crossen JS, ter Riet G, Mol BW, van der Post JA, Leeflang MM, et al. (2009) Are tests for predicting pre-eclampsia good enough to make screening viable? A review of reviews and critical appraisal. *Acta Obstet Gynecol Scand* 88: 758-765.
11. Conde-Agudelo A, Villar J, Lindheimer M (2004) World Health Organization systematic review of screening tests for preeclampsia. *Obstet Gynecol* 104: 1367-1391.
12. Meads CA, Crossen JS, Meher S, Juarez-Garcia A, ter Riet G, et al. (2008) Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling. *Health Technol Assess* 12: 1-270.
13. Lenfant C (2001) Working group report on high blood pressure in pregnancy. *J Clin Hypertens (Greenwich)* 3: 75-88.
14. Lindheimer MD, Taler SJ, Cunningham FG (2008) Hypertension in pregnancy. *J Am Soc Hypertens* 2: 484-494.
15. Angeli E, Verdecchia P, Narducci P, Angeli F (2011) Additive value of standard ECG for the risk prediction of hypertensive disorders during pregnancy. *Hypertens Res* 34: 707-713.
16. Benedetto C, Valensise H, Marozio L, Giarola M, Massobrio M, et al. (1998) A two-stage screening test for pregnancy-induced hypertension and preeclampsia. *Obstet Gynecol* 92: 1005-1011.
17. Giguere Y, Charland M, Bujold E, Bernard N, Grenier S, et al. (2010) Combining biochemical and ultrasonographic markers in predicting preeclampsia: a systematic review. *Clin Chem* 56: 361-375.
18. Lindheimer MD, Katz AI (1973) Sodium and diuretics in pregnancy. *N Engl J Med* 288: 891-894.
19. Hermida RC, Ayala DE (2004) Prognostic value of ambulatory blood pressure measurements for the diagnosis of hypertension in pregnancy. *Expert Rev Cardiovasc Ther* 2: 375-391.
20. Hermida RC, Ayala DE, Mojon A, Fernandez JR, Silva I, et al. (1998) Blood pressure excess for the early identification of gestational hypertension and preeclampsia. *Hypertension* 31: 83-89.
21. Hermida RC, Ayala DE, Iglesias M (2004) Differences in circadian pattern of ambulatory pulse pressure between healthy and complicated pregnancies. *Hypertension* 44: 316-321.
22. Hermida RC, Ayala DE, Mojon A, Fernandez JR, Alonso I, et al. (2000) Blood pressure patterns in normal pregnancy, gestational hypertension, and preeclampsia. *Hypertension* 36: 149-158.