ORIGINAL ARTICLE

Additive value of standard ECG for the risk prediction of hypertensive disorders during pregnancy

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Prediction of hypertensive complications during pregnancy remains limited, especially in healthy and initially normotensive women. We conducted a prospective screening study for hypertensive complications in pregnant women. We studied 221 nulliparous healthy and normotensive women with singleton pregnancies whose first routine visit was carried out before the twelfth week of gestation. We tested several demographic, clinical and laboratory variables as predictors of a composite pool of prespecified events, including gestational hypertension, preeclampsia or eclampsia. We analyzed the potential additive role of ECG in the identification of women at increased risk of hypertensive disorders. Mean age at entry was 30 years. During pregnancy, there were 28 prespecified events (22 women with gestational hypertension, 5 with preeclampsia and 1 with eclampsia). In univariate analyses, blood pressure (BP), weight, body mass index (BMI) and left atrial (LA) abnormality detected by ECG in lead V₁ showed an association with the risk of hypertensive disorders (all $P < 0.05$). In a multivariable analysis, only mean BP (OR: 3.08, 95% confidence interval (CI): 1.61–5.92; $P = 0.001$ for each 10 mm Hg increase) and LA abnormality in lead V₁ (OR: 4.35, 95% CI: 1.84–10.31; $P = 0.001$) were independent predictors of hypertensive disorders. The final model discriminated well between women who developed hypertensive disorders and women who remained normotensive (AUC = 0.75; 95% CI: 0.67–0.84; $P < 0.0001$). This study suggests that standard ECG is valuable to refine risk stratification for hypertensive disorders in initially normotensive pregnant women. LA abnormality, easily detected by simple visual inspection of the traditional ECG, and mean arterial pressure (MAP), allows a rapid and effective risk stratification for hypertensive disorders. *Hypertension Research* (2011) 34, 707–713; doi:10.1038/hr.2011.12; published online 17 February 2011

Keywords: blood pressure; eclampsia; hypertension, pregnancy-induced; pre-eclampsia; risk assessment

INTRODUCTION

Hypertension is a frequent medical problem during pregnancy.^{1–3} Hypertensive disorders in pregnancy may cause maternal and fetal morbidity and they remain a leading source of maternal mortality, along with thromboembolism, hemorrhage and non-obstetric injuries.^{4–6}

Numerous studies evaluated a variety of tests for prediction of hypertensive disorders during pregnancy.^{7–15} Several demographic, clinical and laboratory investigations, usually collected during antenatal visits, have been investigated as potential predictors of hypertensive disorders during pregnancy.^{9–15} However, early prediction of hypertensive disorders remains problematic, especially in healthy and initially normotensive pregnant women.

Maternal age, medical history, BMI and BP are commonly used to predict the risk of hypertensive disorders during pregnancy.^{8,12,14} Other clinical, biophysical and biochemical tests have not been shown to be sufficiently sensitive and specific to be clinically useful as a screening test.

In this context, although standard ECG is frequently performed during pregnancy for evaluation of cardiovascular disorders in pregnant women, its potential additive role in the identification of women

at increased risk of hypertensive disorders over traditional predictors has never been tested.

To this purpose, we developed a prediction model for early identification of women at increased risk of hypertensive disorders during pregnancy by analyzing the combination of simple clinical variables and standard ECG parameters obtained at the first antenatal booking visit before the twelfth week of gestation.

METHODS

This was a prospective screening study for hypertensive complications in pregnant women. All subjects were nulliparous healthy women with singleton pregnancies whose first routine prenatal visit took place before 12 weeks of gestation. Gestational age was determined from the best estimate, according to menstrual history or ultrasound measurement early in pregnancy.

The study was conducted from 1 January 2009 to 28 February 2010. Only nulliparous women who were normotensive (BP < 140 mm Hg systolic and < 90 mm Hg diastolic) at booking were included. Women with chronic hypertension (defined as BP exceeding 140/90 mm Hg before pregnancy or before 20 weeks' gestation) were excluded from the study. A close follow-up was planned to timely identify pregnant women with hypertension and its complications early in pregnancy. We planned 12–14 visits every 2 weeks from the

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Received 1 October 2010; revised 12 December 2010; accepted 26 December 2010; published online 17 February 2011

first prenatal visit to the thirty-sixth week of gestation and then weekly until delivery.

All women gave their informed consent before their inclusion in the study.

At the inclusion visit, medical history, cigarette smoking during pregnancy (yes or no), medications, obstetric and family history were obtained through a questionnaire. A complete clinical examination was also carried out in each woman. Women with conditions associated with a very high risk of pregnancy-induced hypertension (renal disease, multiple pregnancy, diabetes, autoimmune disease, family history of preeclampsia) were not included in the screening program. The maternal weight and height were measured and the BMI was calculated in kg m^{-2} . In addition, BP, standard laboratory tests and ECG were also performed.

BP measurements

BP was measured by our medical staff with a manual mercury sphygmomanometer. Women were allowed to sit quietly for at least 5–10 min before each BP measurement. Measurements were performed in the sitting position, with the cuff positioned at the level of the heart (supine and lateral positions were avoided). Korotkoff sounds I and V were used to denote the systolic and diastolic BP, respectively. An appropriate-sized cuff (length of 1.5 times the circumference of the arm) was used. If BP was higher by more than 10 mm Hg in one of the two arms, the arm with the higher BP was used.

Pulse pressure (PP) was computed by systolic BP–diastolic BP, whereas mean arterial pressure (MAP) was estimated using the following formula: (diastolic BP + (PP/3)).

Laboratory test

Laboratory parameters were assessed using standard techniques and included hemoglobin, fibrinogen, urinalysis, serum sodium, potassium, creatinine and glucose levels, serum lipids (that is, total cholesterol, high-density lipoprotein, low-density lipoprotein and triglycerides). Urinalysis was used as a screen for proteinuria (urine dipstick). Presence of proteinuria was confirmed with a 24-h urine collection (300 mg per day was the reference range for abnormal protein excretion).

ECG

At the first antenatal visit, 12-lead ECG was recorded with 25 mm s^{-1} and 1 mV cm^{-1} calibration. ECG tracings were coded and interpreted by one expert reader (FA) in a central laboratory. The following ECG parameters were analyzed: heart rate (HR), QRS duration (ms), corrected QT interval (ms), Cornell voltage (mm), presence of ST-T abnormalities (Yes *vs.* No) and LA abnormality (Yes *vs.* No).

The QT interval was measured as the time between the start of the Q wave and the end of the T wave and corrected by HR, according to the Bazett's formula.¹⁶

The Cornell voltage was computed as the sum of the amplitudes of S wave in V_3 and R wave in aVL.¹⁷

ST-T changes were analyzed according to the Minnesota Coding.¹⁸ Criteria for ST-T changes were any of the following: (1) coexistence, in any leads I, II, aVL or V_3 – V_6 of ST-segment horizontal or downward sloping depression $\geq 0.05 \text{ mV}$ (code 4-1 or 4-2) plus T-wave asymmetric inversion (code 5-1 or 5-2); (2) ST-J depression $< 0.05 \text{ mV}$ with ST-segment downward sloping and segment or T-wave nadir greater than 0.05 mV below P–R baseline, in any of leads I, II, aVL or V_2 – V_6 (code 4-3); (3) ST-J depression of $\geq 0.10 \text{ mV}$ and ST-segment upward sloping or U-shaped, in any of leads I, II, aVL or V_2 – V_6 (code 4-4); (4) T-wave amplitude zero (flat), negative or diphasic (negative-positive type only) with $< 0.10 \text{ mV}$ negative phase in lead I, II, V_3 – V_6 or in lead aVL when R-wave amplitude is $\geq 0.5 \text{ mV}$ (code 5-3); (5) T-wave amplitude positive and T- to R-wave amplitude ratio $< 1:20$ in any of leads I, II, aVL or V_3 – V_6 when R-wave amplitude in the corresponding leads is $\geq 1.0 \text{ mV}$ (code 5-4).

P-wave morphology was analyzed in all of the standard leads. The criteria used for the diagnosis of P-wave abnormality in lead V_1 were: (1) biphasic interval in deeply notched P wave with (2) terminal forces equal to or more negative than -0.04 mm s , as obtained from the product of the depth of the terminal negative deflection and its duration.^{19,20} The following other criteria were used for the diagnosis of LA abnormality in any other lead than V_1 : (1) biphasic interval in deeply notched P waves wider than 0.04 s or (2)

P-wave/PR-segment ratio greater than 1.6 or (3) P wave higher than 3 mm or (4) total P-wave duration greater than 0.11 s .^{19,20}

Outcomes

The primary outcome of the study was the development of gestational hypertension, preeclampsia 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.

Hypertension in pregnancy was defined as a BP $\geq 140 \text{ mm Hg}$ systolic or $\geq 90 \text{ mm Hg}$ diastolic.^{1–3} Diagnosis of hypertension was on the basis of in-hospital BP measurements and documented on at least two occasions at least 6 h apart. If high BP was recorded, patients were questioned regarding signs and symptoms of end-organ damage or decreased urine output. Supplemental laboratory evaluations were also performed in search of end-organ damage.

Preeclampsia was defined as new onset hypertension and proteinuria (see laboratory test) after 20 weeks of gestation, whereas eclampsia referred to the occurrence of one or more generalized convulsion and/or coma in the setting of preeclampsia and in the absence of other neurologic conditions.^{1–3}

HELLP syndrome was diagnosed by criteria for preeclampsia present together with at least one of the following laboratory findings: elevated serum aspartate transferase greater than 70 U l^{-1} , thrombocytopenia (platelet count less than 100 000) and laboratory evidence of hemolysis.

Placental abruption was defined by uterine tenderness associated with concealed or revealed retroplacental hemorrhage. This diagnosis was only made in the presence of one of the following factors: fetal distress necessitating delivery (or stillbirth), maternal shock (based on maternal BP less than 80 mm Hg systolic and maternal tachycardia) and maternal coagulopathy (thrombocytopenia less than 100 000, together with prolonged international normalized ratio or activated partial thromboplastin time).

Fetal growth restriction was classified according to sex- and gestation-specific birth weight centiles as being: less than fifth centile or fifth–tenth centile.

Premature delivery was defined by gestation at birth less than 37 completed weeks of gestation. Stillbirth was defined by birth of a fetus weighing at least 400 g or at least 20 weeks of gestation that shows no signs of life after birth. Neonatal death was considered when the death of a live-born neonate occurred within 28 days of birth, with birth weight at least 400 g or at least 20 weeks of gestation. Congenital abnormality was considered when the presence of an abnormality was sufficiently serious as to impair the normal neonatal course.

Data analysis

Statistical analysis was performed using SPSS 15 (SPSS, Chicago, IL, USA) and STATA 9 (StataCorp, Lakeway Drive College Station, TX, USA). Data are reported as mean $\pm$ s.d. or percentage, when appropriate. Comparisons between groups were made using one-way analysis of variance or χ^2 when appropriate.

Logistic regression was used to investigate the relationship between the various demographic, clinical, laboratory and ECG parameters and outcomes. We tested a baseline model in order to identify the univariable predictors of hypertensive disorders. Then, we modeled a multivariable logistic model to test the independent prognostic value of those risk factors that proved significant in the univariable analysis.

In addition to standard descriptive and comparative analyses, we also tested the discrimination and calibration of the multivariable prediction model. At this purpose, we used the receiver-operating characteristic curve analysis and the Hosmer–Lemeshow statistic, to examine the prediction value of the model on the occurrence of hypertensive disorders events, to analyze its ability in the identification of pregnant women at increased risk for hypertensive events (ability to distinguish between women that develop hypertensive disorders and women that do not develop hypertensive disorders) and to test agreement between predicted risks and observed frequencies.

RESULTS

Overall, 308 women were screened and 87 excluded (Figure 1). A total of 221 pregnant women were included in the final analysis.

Figure 1 Patients flow diagram.

Main characteristics and outcome

Baseline characteristics of the cohort are reported in Table 1. Mean age was 30 years. Prevalence of dyslipidemia was 3.6%. Current smokers were 5.4%. Baseline BP was 115/71 mm Hg. In all, 82 women (37.1%) had LA abnormality in at least one standard lead; in 61 (27.6%) of these pregnant women LA abnormality was recorded in lead V₁. Other measured ECG parameters are shown in Table 1.

The primary outcome of hypertensive disorders occurred in 28 women. Specifically, gestational hypertension occurred in 22 women, 5 women experienced preeclampsia (3 of these developed HELLP syndrome) and 1 woman had eclampsia. Among pre-eclamptic women, 3 had late-onset preeclampsia (≥ 34 weeks gestation).

The secondary composite outcomes were recorded in 43 women. Multiple events (hypertensive disorders and other maternal or fetal/neonatal complications) were observed in nine women. Overall, premature deliveries occurred in 14 women, 6 women delivered growth-restricted neonates, 2 women experienced placental abruption and 2 congenital heart defect requiring admission to neonatal nursery were recorded. No neonatal deaths were observed.

Study population was subdivided (Table 1) 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, BMI and BP were higher in women with hypertensive diseases than in those without them (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 including LA abnormality observed in other leads than V₁ did not differ between the two groups (Table 1).

Table 1 Main demographic and biochemical characteristics of women with and without development of hypertensive disorders during pregnancy

	Hypertensive disorders			
	All (n=221)	No (n=193)	Yes (n=28)	P
Anthropometric measures				
Age (years)	30.2±5.9	30.1±5.9	31.1±5.8	0.400
Height (cm)	165.7±4.5	165.6±4.7	165.9±3.7	0.749
Weight (kg)	62.6±9.4	61.8±8.8	66.9±11.6	0.008
BMI (kg m ⁻²)	22.8±3.1	22.5±2.8	24.3±4.0	0.005
Medical history				
Current smokers (%)	5.4	5.2	7.1	0.653
Dyslipidemia	3.6	4.1	0.0	0.601
Previous thyroid disease	3.2	3.6	0.0	0.600
Previous use of estrogens (%)	18.6	18.1	21.4	0.613
Blood pressure				
Systolic BP (mm Hg)	115.2±9.1	114.2±7.9	121.8±13.1	<0.0001
Diastolic BP (mm Hg)	70.6±8.0	70.2±7.8	73.4±8.6	0.049
MAP (mm Hg)	85.5±6.9	84.9±6.3	89.5±9.1	0.001
Pulse pressure (mm Hg)	44.5±10.1	44.0±10.1	48.4±10.5	0.030
Laboratory tests				
Haemoglobin (g dl ⁻¹)	11.9±1.2	11.9±1.2	12.0±1.1	0.658
Fibrinogen (mg dl ⁻¹)	403.1±78.3	397.7±70.3	431.9±109.9	0.073
Sodium (mEq l ⁻¹)	137.0±1.8	137.0±1.7	136.7±2.2	0.558
Potassium (mEq l ⁻¹)	4.1±0.4	4.1±0.4	4.1±0.4	0.926
Glucose (mg dl ⁻¹)	79.3±13.1	78.8±13.0	82.9±13.7	0.153
Creatinine (mg dl ⁻¹)	0.60±0.14	0.60±0.14	0.59±0.13	0.678
ECG				
Heart rate (b.p.m.)	82.1±15.2	82.0±15.5	82.2±13.0	0.947
QRS duration (ms)	84.3±7.5	84.2±7.5	85.2±7.7	0.506
Corrected QT interval (ms)	417.2±24.9	416.9±24.9	419.1±24.3	0.670
Cornell voltage (mm)	10.1±4.4	10.1±4.5	10.4±3.8	0.709
ST-T changes (%)	23.7	25.1	14.3	0.244
Left atrial abnormality (%)				
In lead V ₁	27.6	23.8	53.6	0.002
In other lead than V ₁	14.5	14.0	17.9	0.570
In any lead	37.1	34.2	57.1	0.022

Abbreviations: BMI, body mass index; BP, blood pressure; ECG, electrocardiography; MAP, mean arterial pressure.

Predictive model

We tested the following variables as predictors of hypertensive disorders: age (years), height (cm), weight (kg), BMI (kg m⁻²), previous use of estrogens (yes, no), systolic and diastolic BP (mm Hg), MAP (mm Hg), PP (mm Hg), hemoglobin (g dl⁻¹), fibrinogen (mg dl⁻¹), sodium (mEq l⁻¹), potassium (mEq l⁻¹), serum creatinine (mg dl⁻¹), serum glucose (mg dl⁻¹), smoking habit (non-smoker, current smoker), HR (b.p.m.), QTc (ms), Cornell voltage (mm), ST-T changes (yes, no) and LA abnormality (yes, no). Weight, BMI, systolic and diastolic BP, MAP, PP, and LA abnormality in lead V₁ or in any lead were univariable predictors for hypertensive disorders (all $P < 0.05$; Figure 2). Other tested parameters did not achieve statistical significance (all $P > 0.05$).

As shown in Table 2, only MAP and LA abnormality in lead V₁ (Figure 3) were independent predictors of hypertensive disorders at

Figure 2 Univariable predictors of hypertensive disorders during pregnancy.

Table 2 Results of the multivariable analysis for hypertensive disorders during pregnancy

Variable	Comparison	OR (95% CI)	P
MAP (mm Hg)	10 mm Hg	3.08 (1.61–5.92)	0.001
Left atrial abnormality in lead V ₁	Yes vs. No	4.35 (1.84–10.31)	0.001

Abbreviations: CI, confidence interval; MAP, mean arterial pressure; OR, odds ratio.
Hosmer–Lemeshow test: $P=0.346$.

the multivariable analysis. Other covariates tested did not achieve statistical significance and they were not included in the final model. In particular, weight, BMI, LA abnormality in other lead than V₁, diastolic and systolic BP, and PP did not achieve significance to enter a model, including MAP and LA abnormality in lead V₁ as covariates.

The probability of developing hypertensive disorders according to baseline MAP and P-wave morphology (normal vs. LA abnormality in lead V₁) is depicted in Figure 4 (left panel). The formula used to

calculate the risk of hypertensive disorders was: $1/(1+\exp^{-z})$ where $z=(\text{intercept}+(0.112\times\text{MAP})+(1.470\times\text{P-wave morphology in lead V}_1))$. Using this model, the presence of LA abnormality in lead V₁ was associated to a fourfold increased risk of developing hypertensive disorders (OR: 4.35, 95% (CI): 1.84–10.31; $P=0.001$).

We also developed a nomogram to predict probability of hypertensive disorders and to facilitate the practical application of the model (Figure 4, right panel). As an example on how to use this nomogram, 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%.

The calibration of the final model was good, confirmed by a nonsignificant Hosmer–Lemeshow test ($P=0.346$). Moreover, the final model discriminated well between women who developed hypertensive disorders and women who remained normotensive during pregnancy, with an AUC of 0.754 (95% CI: 0.667–0.841; $P<0.0001$).

Figure 3 ECG tracings of a 30-year-old woman who developed gestational hypertension. ECG was performed in the first trimester of pregnancy showing a typical LA abnormality in lead V₁ (biphasic interval in deeply notched P wave in lead V₁ with terminal forces equal to or more negative than -0.04 mm s, as obtained from the product of the depth of the terminal negative deflection and its duration). Minor ST-T changes in leads V₄ and V₅ were also recorded.

Figure 4 Risk of developing hypertensive disorders according to baseline MAP and P-wave morphology in lead V₁ (left panel). For practical application of the model, the normogram for the estimation of the risk of hypertensive disorders is also depicted (right panel).

In addition, the same final multivariable model was tested to predict the secondary outcome (a composite measure of hypertension disorders and other maternal or fetal/neonatal complications): MAP (OR: 2.21, 95% CI: 1.32–3.69 for each 10 mm Hg increase; $P=0.003$) and LA abnormality in lead V₁ (OR: 2.14, 95% CI: 1.05–4.41; $P=0.038$) were confirmed as independent predictors of this outcome (Hosmer–Lemeshow test: $P=0.126$).

Correlates of LAE

Prevalence of LA abnormality in lead V₁ was higher in women with development of hypertensive disorders (53.6%) than in women who remained normotensive during pregnancy (23.8%; $P=0.002$).

Compared with women with normal P wave at ECG, women with LA abnormality in lead V₁ had similar MAP (85.6 vs. 85.1 mm Hg, $P=0.661$).

Prevalence of LA abnormality in lead V₁ did not show any associations with baseline BP values. According to quartiles of MAP distribution (cutoff levels: 80, 85 and 91 mm Hg), prevalence of LA abnormality in lead V₁ were 32, 22, 39 and 20% ($P=0.072$ for trend). Similar results were obtained for diastolic and systolic BP (all $P>0.05$).

DISCUSSION

Using the combination of baseline MAP measurement and analysis of P-wave morphology in lead V₁ at ECG obtained from initially

normotensive women at the antenatal booking visit before 12 weeks of gestation, we developed a prediction model that allowed an early identification of women at high risk for hypertensive disorders during pregnancy. After adjustment for baseline MAP, women with LA abnormality in lead V₁ showed a remarkable fourfold increased risk for hypertensive disease (OR: 4.35, 95% CI: 1.84–10.31; $P=0.001$). 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.

Abnormality of P-wave morphology tested in our analysis 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.

LA enlargement and hypertension in pregnancy

LA enlargement is very common in hypertensive subjects and may be an early sign of heart involvement in arterial systemic hypertension.^{21,22} Although some echocardiographic studies showed that women developing hypertensive complications during pregnancy may have different LA dimensions than controls,^{23–26} the potential link between LA abnormality detected early in pregnancy by echocardiography or ECG and development of hypertensive disorders remains elusive. However, some possible mechanisms are supported by epidemiological data and experimental models.

The influence of arterial systemic hypertension on LA enlargement and the close relation of BP with LA dimensions have been extensively investigated. Several studies in hypertensive patients found a significant relation between BP overload and LA abnormalities.^{21,22,27–29} An association between systolic BP levels and LA size has been reported in a large population-based cohort of hypertensive subjects.²⁹ The lack of association between ECG LA enlargement and BP values observed in our study supports the poor ability of casual BP measurements obtained at the time of the first visit to the hospital to detect the real BP load of pregnant women. BP typically falls early in gestation and is usually 10 mm Hg below baseline in the second trimester.³⁰ The fall in BP is induced by a reduction in systemic vascular resistance, which appears to parallel the changes in afterload. The tendency of BP to decrease in early pregnancy may mask the real BP load of women with abnormal BP before pregnancy and reduce the clinical impact of prediction model for hypertensive disorders on the basis of office BP measurements. It is well recognized that a relatively large proportion of pregnant women may have masked gestational hypertension, undetected by office BP measurements, but revealed by specific BP index or circadian patterns computed with ambulatory BP monitoring.^{31–33} Notably, 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.³³ At the same time, night-time ambulatory BP is an independent predictor of LA size in hypertensive patients.³⁴ In this context, the presence of an abnormal P wave at ECG in the early phase of gestation could be considered as a marker of high or high-normal BP values in women with normal BP detected in the office, and consequently refine the predicted risk of hypertensive disorders.

Other potential explanations for the association between LA enlargement and subsequent development of hypertension during pregnancy may be postulated, considering some data obtained from experimental models during pre-eclamptic disease.

Expansion of blood volume directly affects LA pressure and dimensions,³⁵ with a consequent increased release of atrial natriuretic

peptide.³⁶ In pregnancy, the major hemodynamic changes include an increase in cardiac output, and sodium and water retention leading to blood volume expansion. These changes begin early in pregnancy, reach their peak during the second trimester and then remain relatively constant until delivery.^{37,38} In uncomplicated pregnancy, plasma renin activity tends to be increased and atrial natriuretic peptide levels are slightly reduced.^{39,40} In contrast, plasma atrial natriuretic peptide concentrations have been extensively reported as increased in patients with hypertensive disorders during pregnancy, especially in patients with severe preeclampsia.^{41–43}

In this context, the detection of LA enlargement at ECG may be a marker of an abnormal expansion of blood volume in the early phase of pregnancy, which may affect LA dimensions and pressure³⁵ with a consequent increased release of atrial natriuretic peptide. These may predispose to the development of hypertension disease.

Other changes during pregnancy include early renal vasodilatation and hyperfiltration, and marked stimulation of the all measured elements of the renin–angiotensin–aldosterone system.³

In patients developing preeclampsia, there is a loss of the normal pregnancy-associated refractoriness to pressor agents, and the sensitivity to infused angiotensin II increases weeks before overt disease. Explanations for the increased reactivity to angiotensin II include upregulation of receptor sensitivity, synergy with circulating autoantibodies agonistic to the angiotensin type 1 receptor and decreases in the level of circulating Angiotensin 1–7.⁴⁴

As experimental approaches have been confirmed that the local renin–angiotensin–aldosterone system in the heart could trigger development of cardiac hypertrophy⁴⁵ and massive enlargement of the atria caused by myocyte hyperplasia,⁴⁶ an increased sensitivity to the pressor effect of the renin–angiotensin–aldosterone system in some women may be involved in the development of ECG signs of LA enlargement and predisposes to the development of hypertensive disorders.

Comparison with previous studies

Standard ECG is frequently performed during pregnancy. However, there is paucity of data on its ability to identify women at increased risk of hypertensive complications.^{47,48} In a previous prospective study,⁴⁸ women who developed eclampsia had significantly higher mean HR, higher QTc and higher frequency of T-axis deviation. In contrast, a recent analysis in 64 pregnant women showed that pregnancies with abnormal uterine perfusion that developed pathological outcomes showed a trend towards shorter QTc intervals compared with pregnant women with normal perfusion.⁴⁹

Our study did not confirm HR, QTc and ST-T changes as predictors of hypertensive disease during pregnancy.

Similarly to previous studies, we did not have enough data on BP before pregnancy; hence, we could not exclude that some women included in our study had chronic hypertension masked by the physiological fall in BP usually observed in the early phases of pregnancy. However, the prediction model remained suitable in women classified as normotensive by office BP in the first antenatal visit for its potential ability to detect subjects with masked hypertension and at increased risk of hypertensive disorders.

Finally, the technique for BP measurements used in our study needs to be detailed. BP was measured by our medical staff with a manual mercury sphygmomanometer and an appropriate-sized cuff (length of 1.5 times the circumference of the arm) was used. It is well known that the use of a standard cuff width⁵⁰ or of automated oscillometric devices⁵¹ underestimate BP of pregnant women and may affect the correct evaluation of BP during pregnancy.

Conclusions

LA abnormality detected by ECG in lead V₁ is an independent predictor of hypertensive disorders during pregnancy. This study strongly supports the role of standard ECG to refine risk stratification for hypertensive disorders in initially normotensive pregnant women. Even in the absence of digital-specific devices making complex analyses, the presence of LA abnormality in lead V₁ can be easily detected by simple visual inspection of the traditional ECG (Figure 3). It allows, in combination with MAP, the identification of women at increased risk of hypertensive disorders during pregnancy.

Limitations

Our predictive model needs to be validated in larger cohorts of pregnant women before implementation on a clinical setting. In addition, the predictive value of LA abnormality in lead V₁ for the development of hypertensive disorders during pregnancy should be tested over and beyond other accredited risk markers (uterine artery Doppler parameters, ambulatory BP and maternal morphological parameters measured by echocardiography).^{1,2,7,44}

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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