Gestational hypertension risk evaluation based on epidemiological, biochemical, and hemodynamic factors

L. Yang[1], W. Zhang[2], L. Zhang[3], S. Zhang[1], Y. Yang[1], Q. Wang[2], J. Shao[3], G. Chen[3], Y. Wang[3]

[1]College of Life Science and Bioengineering, Beijing University of Technology, Beijing
[2]Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing; [3]Beijing YES Medical Device Co., Ltd., Beijing (China)

Summary

Purpose: Gestational hypertension (GH) is a serious health hazard for pregnant women and fetuses. The incidence of GH involves many epidemiological, biochemical, and hemodynamic factors. *Methods:* The current study investigated the GH risk under the influence of epidemiological, biochemical, and hemodynamic factors, and designed corresponding GH risk evaluation methods and apparatus. *Results:* The evaluation method has 74.15% sensitivity and 81.84% specificity. The ROC area under the curve is 0.841. The apparatus automatically imports epidemiological, biochemical, and hemodynamic factors, and then expresses the GH risk as numbers, bar codes, and colors through logic array analysis. *Conclusion:* The GH risk value can effectively give the risk level of GH. The GH risk barcode can improve the degree of automation of information storage, transmission, and identification in GH monitoring. The GH risk color can also improve the GH macro description.

Key words: Risk factors; Logistic regression; Logic switch array; Risk value; Risk bar code.

Introduction

Gestational hypertension (GH) is a serious health hazard for pregnant women and fetuses [1]. The incidence of GH involves many epidemiological factors. Pregnant women at a high gestational age (GA) [1, 2], are obese [1, 3, 4], have multiple pregnancies (MP) [5, 6], are positive for previous pregnancy-induced hypertension (P-PIH) [1], or have a spontaneous abortion history (SAH) [7, 8] have increased GH risk. The incidence of GH also involves many biochemical factors [3, 9]. Blood testing is a routine prenatal examination. Current studies report that pregnant women with GH have significantly different mean platelet volumes (MPV) [10-12], platelet count (PLT) [13, 14], and hematocrit (HCT) [15, 16] compared with normal pregnant women. In addition, the incidence of GH concerns many hemodynamic factors [17-22]. Pregnant women with GH have different hemodynamic changes compared with normal pregnant women, as detected through a non-invasive hemodynamic monitoring device produced by Beijing YES Medical Device Co., Ltd (China). Changes in the total peripheral resistance (TPR) and pulse waveform characteristic value (PWCV) are significantly correlated with GH risk [23-25].

The uterine artery resistance score (UARS) [26] and the nomogram method [27] are two GH risk evaluation techniques. Four indicators, namely, blood flow pulsatility indices, [28] resistance indices [29], systolic and diastolic blood flow velocity ratios (S/D), and early diastolic notch [30] of both sides of the maternal uterine artery are detected using color Doppler ultrasound at 24 to 25 weeks of gestation. UARS was established in the current study. The nomogram method entails setting the parity, previous preeclampsia, chronic hypertension, diastolic blood pressure, and proteinuria at certain values, with each value corresponding to the possible percentage of the corresponding risk. The final sum is then calculated as the GH risk.

UARS and the nomogram method have certain shortcomings. UARS only takes hemodynamic factors of GH into account and does not consider the epidemiological and biochemical factors. Therefore, the single score on the GH risk expression has some deviations. The nomogram method has more test parameters compared with UARS but does not consider the epidemiologic, biological, and hemodynamic factors in contributing to GH risk expression.

Therefore, the incidence of GH is affected by epidemiological, biochemical, and hemodynamic factors. However, GH risk evaluation methods are mostly one-sided, non-diverse, and noncomprehensive. In the current study, the GH results under the influence of epidemiological, biochemical, and hemodynamic factors were investigated, and GH risk evaluation methods and apparatus based on the foregoing factors were designed.

Methods and Results

GH risk evaluation method

In the present study, 751 pregnant women from the Beijing Obstetrics and Gynecology Hospital, a large maternity unit in China, were the research subjects. All pregnant women were requested to proceed with the first measurement. Those who had no concurrent obstetric or medical problems, such as cardiac disease, chronic hypertension, chronic illness, or long-

Revised manuscript accepted for publication February 23, 2012

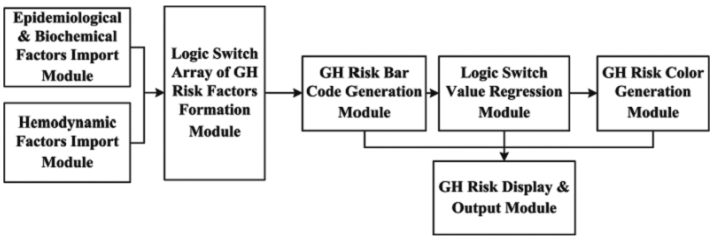

Figure 1. — Structure chart of GH risk evaluation apparatus based on epidemiological, biochemical and hemodynamic factors.

Figure 2. — A typical example of GH risk bar code generated by GH risk bar code generating module.

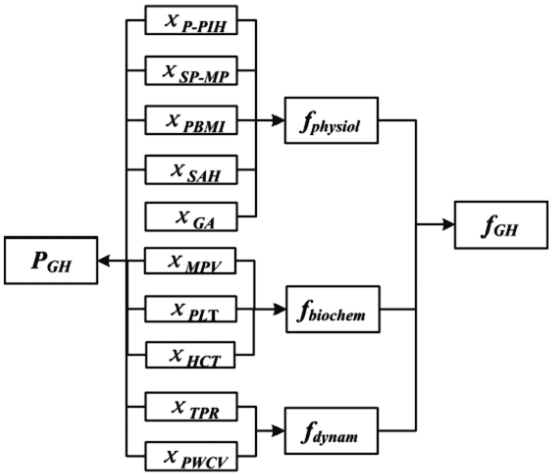

Figure 3. — Logic switch value regression module.

term use of medication, were accepted. All subjects had nulliparous pregnancies. All pregnancies were dated from the last menstrual period and ultrasound examination before the 12th week of gestation. The examinations were performed at 4-week intervals from the prenatal visit until delivery. After completion of the study, only pregnancies with entirely uneventful courses were selected and added to the normal group. Pregnancies diagnosed with GH were added to the GH group. The diagnosis criterion of GH was adopted according to the recommendation of Danforth in Obstetrics and Gynecology, 3rd edition. Up to 457 patients were included in the normal group and 294 were placed in the GH group.

The epidemiological data included P-PIH, singleton pregnancy or multiple pregnancies (SP-MP), progestational body mass index (PBMI), SAH, and GA. The biochemical factors included MPV, PLT, and HCT. The hemodynamic factors included TPR and PWCV.

The data were analyzed using the chi-square test, nonmatched case control study, odds ratio (OR) value, and 95% confidence interval to determine the factors in the pathogenesis of GH. Multivariate logistic regression analysis was used, and all statistical calculations were performed using the SPSS15.0 software.

The quantitative method used to determine the GH risk factors is shown in Table 1. The OR value of each risk factor was used to reflect the incidence probability of GH. The results are shown in Table 2. After these factors underwent logistic regression analysis, GA was discarded in a stepwise regression. The final regression equation was as follows:

$$LogitP = -3.055+2.274\chi_{P\text{-}PIH}+2.161\chi_{SP\text{-}MP}+1.625\chi_{PBMI}+1.455\chi_{SAH} -1.526\chi_{MPV}+0.670\chi_{PLT}-0.575\chi_{HCT}+2.283\chi_{TPR}+1.099\chi_{PWCV}$$

The chi-square test yielded the values $\chi^2 = 311.296$, $p < 0.05$. The logistic regression equations were statistically significant. The probability of GH occurrence (PGH) was calculated using the formula below, and ROC curve analysis was performed. The ROC area was 0.841, the standard error was 0.016, and the 95% confidence intervals were 0.810-0.872.

$$P_{GH} = \frac{e^{LogitP}}{1 + e^{LogitP}}$$

GH risk evaluation apparatus

A GH risk evaluation method based on epidemiological, biochemical, and hemodynamic factors was established. The epidemiological, biochemical, and hemodynamic factors of pregnant women were synthetically considered and logically quantified. The GH risk was expressed as the GH risk value, GH risk bar code, and GH risk color. The GH risk evaluation apparatus included seven modules, namely, the epidemiological and biochemical factor import module, the hemodynamic factor import module, the logic switch array of GH risk factor formation module, the GH risk bar code generation module, the logic switch value regression module, the GH risk color generation module, and the GH risk display and output module.

As shown in Figure 1, the epidemiological, biochemical, and hemodynamic factors were imported from the epidemiological and biochemical factor import module and hemodynamic factor import module. The logical switch value of each factor was formatted using the logic switch array of the GH risk factor formation module; the GH risk bar code was generated by the GH risk bar code generation module; the GH risk value was computed by the logic switch value regression modules; and the GH risk color was generated by the GH risk color generation module. The final GH risk value, bar code, and color were exported on the display apparatus through the GH risk display and output module.

The epidemiological and biochemical factors of the pregnant women were exported into the epidemiological and biochemical factor import module, and the hemodynamic factors were imported into the hemodynamic factor import module.

The logic switch array of the GH risk factor formation module consists of logic switches for the epidemiological, biochemical, and hemodynamic factors. The logic switches for the epidemiological factors were P-PIH, SP-MP, PBMI, SAH, and GA alternately, with logic switch values of $X_{P\text{-}PIH}$, $X_{SP\text{-}MP}$, X_{PBMI}, X_{SAH}, and X_{GA}, respectively. The logic switches of the biochemical factors were MPV, PLT, and HCT alternately, with logic switch values of X_{MPV}, X_{PLT}, and X_{HCT}, respectively. The logic switches of the hemodynamic factors were TPR and PWCV, with logic switch values of X_{TPR} and X_{PWCV}, respectively.

The logic switch value of each logic switch was 1 when the logic switch was turned on and 0 when the logic switch was turned off. The conditions for the logic switches and the corresponding logic values are shown in Table 1.

Table 1. — *Quantitative method of GH risk factors.*

GH risk factors/ Logic switch	Logic switch value	Quantitative method
P-PIH	$X_{P\text{-}PIH}$	P-PIH positive, $X_{P\text{-}PIH} = 1$; P-PIH negative, $X_{P\text{-}PIH} = 0$
SP-MP	$X_{SP\text{-}MP}$	Multiple pregnancies, $X_{SP\text{-}MP} = 1$; Singleton pregnancy, $X_{SP\text{-}MP} = 0$
PBMI	X_{PBMI}	PBMI ≥ 0.24 kg/cm^2, $X_{PBMI} = 1$; PBMI < 0.24 kg/cm^2, $X_{PBMI} = 0$
SAH	X_{SAH}	SAH positive, $X_{SAH} = 1$; SAH negative, $X_{SAH} = 0$
GA	X_{GA}	GA ≥ 35, $X_{GA} = 1$; GA < 35, $X_{GA} = 0$
MPV	X_{MPV}	MPV positive, $X_{MPV} = 1$; MPV negative, $X_{MPV} = 0$
PLT	X_{PLT}	PLT positive, $X_{PLT} = 1$; PLT negative, $X_{PLT} = 0$
HCT	X_{HCT}	HCT positive, $X_{HCT} = 1$; HCT negative, $X_{HCT} = 0$
TPR	X_{TPR}	TPR ≥ 1.2, $X_{TPR} = 1$; TPR < 1.2, $X_{TPR} = 0$
PWCV	X_{PWCV}	PWCV ≥ 0.4, $X_{PWCV} = 1$; PWCV < 0.4, $X_{PWCV} = 0$

Table 2. — *Multiple factors analysis results of GH.*

Logic switch value	χ^2	p	OR	95% CI (OR)
$X_{P\text{-}PIH}$	3.110	0.078	9.718	0.776~121.687
$X_{SP\text{-}MP}$	14.259	0.000	8.679	2.827~26.644
X_{PBMI}	51.085	0.000	5.079	3.253~7.931
X_{SAH}	10.427	0.001	4.283	1.771~10.355
X_{GA}	9.105	0.003	1.693	1.203~2.384
X_{MPV}	52.343	0.000	4.602	3.043~6.985
X_{PLT}	2.897	0.089	1.954	0.903~4.226
X_{HCT}	3.756	0.053	0.563	0.315~1.007
X_{TPR}	52.764	0.000	9.809	5.297~18.163
X_{PWCV}	10.708	0.001	3.002	1.554~5.800

The GH risk bar code was generated from the GH risk bar code generation module in the order X_s, X_{TPR}, $X_{P\text{-}PIH}$, $X_{SP\text{-}MP}$, X_{PBMI}, X_{MPV}, X_{SAH}, X_{PWCV}, X_{PLT}, X_{GA}, X_{HCT}, and X_e. X_s and X_e are the logic switch values of the start and end tag switches, respectively. X_s was 1 and X_e was 0. Figure 2 shows a typical example of a GH risk bar code generated by the module, where the GH risk bar code was 110011100010 based on the X_{TPR}, X_{PBMI}, X_{MPV}, X_{SAH}, X_{PWCV}, and X_{HCT} logic switch values, which were all 1. The $X_{P\text{-}PIH}$, $X_{SP\text{-}MP}$, X_{PWCV}, X_{GA}, and X_{HCT} logic switch values were 0.

The logic switch value regression module is shown in Figure 3. The GH risk bar code was imported, whereas the $X_{P\text{-}PIH}$, $X_{SP\text{-}MP}$, X_{PBMI}, X_{SAH}, X_{GA}, X_{MPV}, X_{PLT}, X_{HCT}, X_{TPR}, and X_{PWCV} logic switch values were exported. The epidemiological risk value $f_{physiol}$, the biochemical risk value $f_{biochem}$, the hemodynamic risk value f_{dynam}, and the GH risk value f_{GH} were generated using the following formula:

$$f_{physiol} = P_1 \div_{P\text{-}PIH} + P_2 \div_{MP} + P_3 \div_{PBMI} + P_4 \div_{SAH} + P_5 \div_{GA}$$

$$f_{biochem} = B_1 \div_{MPV} + B_2 \div_{PLT} + B_3 \div_{HCT}$$

$$f_{dynam} = D_1 \div_{TPR} + D_2 \div_{PWCV}$$

$$f_{GH} = f_{physiol} + f_{biochem} + f_{dynam}$$

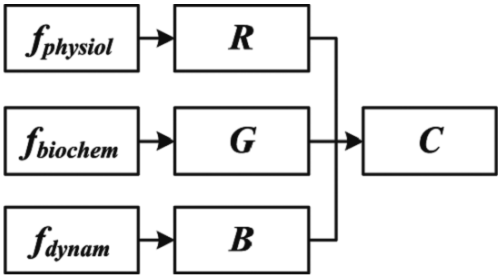

Figure 4. — GH risk color generation module.

Where P_1, P_2, P_3, P_4, P_5, B_1, B_2, B_3, D_1, and D_2 are the OR values of the corresponding factors.

The GH risk color-generating module is shown in Figure 4. The epidemiological risk value $f_{physiol}$ corresponds to the red value R; the biochemical risk value $f_{biochem}$, to the green value G; the hemodynamic value f_{dynam}, to the blue value B; and the GH risk value f_{GH}, to the color value C constructed by the red, green, and blue values R, G, and B, respectively. The GH risk color was generated by the color value C. R, G, and B is hexadecimal numbers generated by the following formula:

$$R = 255 - \frac{255 f_{physiol}}{P_1 + P_2 + P_3 + P_4 + P_5},$$

$$G = 255 - \frac{255 f_{biochem}}{B_1 + B_2 + B_3},$$

$$B = 255 - \frac{255 f_{dynam}}{D_1 + D_2},$$

Where C is the $\{R, G, B\}$ sequence.

The final GH risk value, bar code, and color were exported on the display apparatus through the GH risk display and output module.

Discussion

Gestational age (GA) above 30 years is a risk factor for preeclampsia superimposed on chronic hypertension and a protective factor against preeclampsia [1]. Thadhani *et al.* [32] found that obese pregnant women have a more increased risk of GH than non-obese women. Compared with women with a pregravid BMI of 21-22.9 kg/m^2, the relative risk of GH was 1.6 for women with BMI of 23-24.9 kg/m^2, 2.0 for BMI 25-29.9 kg/m^2, and 2.6 for BMI over 30 kg/m^2. Multiple pregnancies are another risk factor for GH. The logistic regression shows that twin pregnancy carries a relative risk of 3.5 [33]. Other studies showed that a positive family history of hypertension, hypercholesterolemia, chronic hypertension, and gestational diabetes are closely related to increased risk of GH [34-36].

Pregnant women with TPR greater than or equal to 1.2 and with PWCV greater than or equal to 0.4 have significantly higher GH incidence. The results were 76.9% sen-

sitivity and 74.7% specificity [24]. Yu *et al*. [37] developed a predictive model for preeclampsia and found that the combination of uterine artery Doppler ultrasound and maternal factors provides the best estimate of risk. Gomez *et al*. [38] analyzed the uterine artery Doppler at 11-14 weeks of gestation to screen for hypertensive disorders and associated complications in an unselected population. They produced a scoring system with a sensitivity of 23.9% and a specificity of 93.8% to screen all complications of a mean PI > 95th percentile, which was found in 53/999 pregnancies. In the screening for preeclampsia, the detection rate for a 5% false-positive rate was 14.1% for PAPP-A, 54.7% for uterine artery mean PI, and 62.1% for a combination of PAPP-A and uterine artery mean PI [39]. Lee *et al*. [40] integrated a multifactorial model based on mid-trimester beta-hCG levels for the prediction of severe preeclampsia, with a sensitivity of 70% and a specificity of 71%. The mean MSuE [3] levels in patients with early onset were significantly lower than in patients with late-onset severe preeclampsia. High MSAFP and hCG and low MSuE [3] may be significant markers of early- rather than late-onset severe preeclampsia [41].

UARS has four indicators, namely, the blood flow pulsatility indices, resistance indices, systolic and diastolic blood flow velocity ratios (S/D), and early diastolic notch of both sides of the maternal uterine artery. The UARS for the prediction of PIH also appeared statistically significant ($p < 0.01$), with its optimal cutoff level ≥ 4 scores. The value of UARS for the prediction of PIH was much higher than that of other single parameters, with 50% sensitivity and 98.9% specificity [26]. Deis *et al*. [27] created a nomogram for the individual prediction of preeclampsia based on multivariate analysis, nulliparity, previous preeclampsia, diastolic blood pressure, biparietal diameter, and umbilical artery Doppler resistance index which were introduced into a nomogram with an area under the ROC curve = 0.73.

Therefore, GH risk evaluation methods and apparatus were established by considering the high risk factors of GH, including epidemiological, biochemical, and hemodynamic factors. The risk factors were quantified, valuated, and demonstrated in the evaluation apparatus. The sensitivity and specificity were 74.15% and 81.84%. The ROC area under the curve was 0.841. The combination of epidemiological, biochemical, and hemodynamic factors in evaluating the risk of GH produced better results than the single-factor evaluation method. The evaluation methods and apparatus may determine the possible occurrence of GH for early intervention and for reduction of maternal and child hazards.

Conclusion

GH risk evaluation methods and apparatus based on epidemiological, biochemical, and hemodynamic factors were proposed. The GH risk evaluation methods and apparatus automatically imported epidemiological, biochemical, and hemodynamic factors from the case management computer, monitored the GH noninvasive hemodynamic factors, and expressed the GH risk as values, bar codes, and colors through logic array analysis. The GH risk values, including P_{GH} and f_{GH}, can effectively yield the GH risk level, which is important for early prediction, early detection, and early intervention of GH and for improving the quality of perinatal care. The GH risk bar code can improve the degree of automation of data storage, transmission, and identification in GH monitoring. The GH risk color can improve the macro description of the GH risk.

Acknowledgments

We thank Dr. Gingqnig Wu, Dr. Xin Feng and Dr. Changdong Li from Beijing Obstetrics and Gynecology Hospital and Xuwen Li from Beijing University of Technology for their support and help in the study. Their grant for the study in Beijing Obstetrics and Gynecology Hospital and Beijing University of Technology is gratefully acknowledged. This work was supported by the Science and Technology Project of Beijing [Z0005190042011], Research Fund of Capital Medical Development [2005-2011] and National Nature Science Foundation of China [30672238].

References

[1] Assis T.R., Viana F.P., Rassi S.: "Study on the major maternal risk factors in hypertensive syndromes". *Arq. Bras. Cardiol*., 2008, *91,* 11.
[2] Usta I.M., Nassar A.H.: "Advanced maternal age. Part I: Obstetric Complications". *Am. J. Perinatol*., 2008, *25,* 521.
[3] Dane B., Dane C., Kiray M., Koldas M., Cetin A.: "A new metabolic scoring system for analyzing the risk of hypertensive disorders of pregnancy". *Arch. Gynecol. Obstet.,* 2009, *280*, 921.
[4] Bodnar L.M., Catov J.M., Klebanoff M.A., Ness R.B., Roberts J.M.: "Prepregnancy body mass index and the occurrence of severe hypertensive disorders of pregnancy". *Epidemiology,* 2007, *18,* 234.
[5] Selvaggi L., Loverro G., Schena F.P., Manno C., Cagnazzo G.: "Long-term follow-up of women with hypertension in pregnancy". *Int. J. Gynaecol. Obstet*., 1988, *27,* 45.
[6] Elster N.: "Less is more: the risks of multiple births. The institute for science, Law, and technology working group on reproductive technology". *Fertil. Steril*., 2000, *74,* 617.
[7] Zhao W., Wang J.H.: "Screening program and risk factors on pregnancy-induced hypertension syndrome". *Zhonghua Liu Xing Bing Xue Za Zhi,* 2004, *25,* 845.
[8] Khaskheli M., Baloch S., Baloch A.S.: "Risk factors in early pregnancy complications". *J. Coll. Physicians Surg. Pak*., 2010, *20,* 744.
[9] Robins J.B., Woodward M., Lowe G., McCaul P., Cheyne H., Walker J.J.: "First trimester maternal blood rheology and pregnancy induced hypertension". *J. Obstet. Gynaecol*., 2005, *25,* 746.
[10] Yin S.M., Li Y.Q., Xie S.F., Ma L.P., Wu Y.D., Nie D.N. *et al.:* "Study on the variation of platelet function in pregnancy induced hypertension and gestational diabetes mellitus". *Zhonghua Fu Chan Ke Za Zhi,* 2005, *40,* 25.
[11] Walker J.J., Cameron A.D., Bjornsson S., Singer C.R., Fraser C.: "Can platelet volume predict progressive hypertensive disease in pregnancy?". *Am. J. Obstet. Gynecol.,* 1989, *161,* 676.
[12] Rosevear S.K., Liggins G.C.: "Platelet dimensions in pregnancy-induced hypertension". *N.Z. Med. J.,* 1986, *99,* 356.
[13] Rosevear S.K., Liggins G.C.: "Platelet count in 100 cases of pregnancy induced hypertension". *Mymensingh Med. J*., 2010, *19*, 5.
[14] Mohapatra S., Pradhan B.B., Satpathy U.K., Mohanty A., Pattnaik J.R.: "Platelet estimation: its prognostic value in pregnancy induced hypertension". *Indian J. Physiol. Pharmacol.,* 2007, *51,* 160.

[15] Goh J.T.: "First antenatal visit haematocrit and pregnancy induced hypertension". *Aust. N.Z. J. Obstet. Gynaecol.,* 1991, *31*, 317.
[16] Yu S.Q.: "Hemorrheology and microcirculation in women with pregnancy-induced hypertension". *Zhonghua Fu Chan Ke Za Zhi,* 1990, *25,* 322.
[17] Shirai K., Song M., Suzuki J., Kurosu T., Oyama T., Nagayama D. *et al.:* "Contradictory effects of β1- and α1- aderenergic receptor blockers on cardio-ankle vascular stiffness index (CAVI)-CAVI independent of blood pressure". *J. Atheroscler. Thromb.,* 2011, *18*, 49.
[18] Dyer R.A., Piercy J.L., Reed A.R., Strathie G.W., Lombard C.J., Anthony J.A. *et al.:* "Comparison between pulse waveform analysis and thermodilution cardiac output determination in patients with severe pre-eclampsia". *Br. J. Anaesth.,* 2011, *106*, 77.
[19] Khalil A., Jauniaux E., Harrington K.: "Antihypertensive therapy and central hemodynamics in women with hypertensive disorders in pregnancy". *Obstet. Gynecol.*, 2009, *113,* 646.
[20] Robb A.O., Mills N.L., Din J.N., Smith I.B., Paterson F., Newby D.E. *et al.:* "Influence of the menstrual cycle, pregnancy, and preeclampsia on arterial stiffness". *Hypertension,* 2009, *53,* 952.
[21] Khalil A., Jauniaux E., Cooper D., Harrington K.: "Pulse wave analysis in normal pregnancy: a prospective longitudinal study". *PLoS One,* 2009, *4*, e6134.
[22] Khalil A.A., Cooper D.J., Harrington K.F.: "Pulse wave analysis: a preliminary study of a novel technique for the prediction of pre-eclampsia". *BJOG,* 2009, *116,* 268.
[23] Mei S., Gu H., Wang Q., Zhang S., Zeng Y.: "Pre-eclampsia outcomes in different hemodynamic models". *J. Obstet. Gynaecol. Res.*, 2008, *34*, 179.
[24] Gu H., Zhang S., Qiao Y., Luo Z., Zeng Y., Wang Q.: "A study of maternal hemodynamic change during healthy pregnancy and women with gestation hypertension". *Biomed. Mater. Eng.,* 2006, *16*, 77.
[25] Song J., Zhang S., Qiao Y., Luo Z., Zhang J., Zeng Y. *et al.*: "Predicting pregnancy-induced hypertension with dynamic hemodynamics". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2004, *117*, 162.
[26] Liu W., Lin Q.D., Xia J.G.: "Scoring of uterine arterial resistance for prediction of pregnancy induced hypertension syndrome". *Prog. Obstet. Gynecol.*, 2004, *4,* 266.
[27] Deis S., Rouzier R., Kayem G., Masson C., Haddad B.: "Development of a nomogram to predict occurrence of preeclampsia". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2008, *137*, 146.
[28] Albaiges G., Missfelder-Lobos H., Lees C., Parra M., Nicolaides K.H.: "One-stage screening for pregnancy complications by color Doppler assessment of the uterine arteries at 23 weeks' gestation". *Obstet. Gynecol.*, 2000, *96,* 559.
[29] Frusca T., Soregaroli M., Valcamonico A., Guandalini F., Danti L.: "Doppler velocimetry of the uterine arteries in nulliparous women". *Early Hum. Dev.*, 1997, *48*, 177.
[30] Irion O., Massé J., Forest J.C., Moutquin J.M.: "Prediction of pre-eclampsia, low birthweight for gestation and prematurity by uterine artery blood flow velocity waveforms analysis in low risk nulliparous women". *Br. J. Obstet. Gynaecol.,* 1998, *105,* 422.
[31] Danforth D.N.: "Obstetrics and Gynecology". Medical Dept., Harper & Row., 1977, 156.
[32] Thadhani R., Stampfer M.J., Hunter D.J., Manson J.E., Solomon C.G., Curhan G.C.: "High body mass index and hypercholesterolemia: risk of hypertensive disorders of pregnancy". *Obstet. Gynecol.*, 1999, *94,* 543.
[33] Coonrod D.V., Hickok D.E., Zhu K., Easterling T.R., Daling J.R.: "Risk factors for preeclampsia in twin pregnancies: a population-based cohort study". *Obstet. Gynecol.*, 1995, *85,* 645.
[34] Ros H.S., Cnattingius S., Lipworth L.: "Comparison of risk factors for preeclampsia and gestational hypertension in a population-Based cohort study". *Am. J. Epidemiol.,* 1998, *147*, 1062.
[35] Roes E.M., Sieben R., Raijmakers M.T., Peters W.H., Steegers E.A.: "Severe severe preeclampsia is associated with a positive family history of hypertension and hypercholesterolemia". *Hypertens Pregnancy,* 2005, *24,* 259.
[36] Innes K.E., Wimsatt J.H., Mcduffie R.: "Relative glucose tolerance and subsequent development of hypertension in pregnancy". *Obstet. Gynecol.*, 2001, *97,* 905.
[37] Yu C.K., Smith G.C., Papageorghiou A.T., Cacho A.M., Nicolaides K.H.: "An integrated model for the prediction of preeclampsia using maternal factors and uterine artery Doppler velocimetry in unselected low-risk women". *J. Obstet. Gynecol.,* 2005, *193,* 429.
[38] Figueras F., Del Río M., Borobio V., Puerto B., Coll O., Cararach V. *et al.:* "Uterine artery Doppler at 11-14 weeks of gestation to screen for hypertensive disorders and associated complications in an unselected population". *Ultrasound Obstet. Gynecol.,* 2005, *26,* 490.
[39] Spencer K., Yu C.K., Cowans N.J., Otigbah C., Nicolaides K.H.: "Prediction of pregnancy complications by first-trimester maternal serum PAPP-A and free beta-hCG and with second-trimester uterine artery Doppler". *Prenat. Diagn.*, 2005, *25,* 949.
[40] Lee L.C., Sheu B.C., Shau W.Y., Liu D.M., Lai T.J., Lee Y.H. *et al.:* "Mid-trimester beta-hCG levels incorporated in a multifactorial model for the prediction of severe pre-eclampsia". *Prenat. Diagn.*, 2000, *20,* 738.
[41] Shenhav S., Gemer O., Sassoon E., Volodarsky M., Peled R., Segal S.: "Mid-trimester triple test levels in early and late onset severe pre-eclampsia". *Prenat. Diagn.*, 2002, *22,* 579.

Address reprint requests to:
L. YANG, M.D., Ph.D.
Bioelectronics and Instruments Lab.
College of Life Science and Bioengineering
Beijing University of Technology
Pingleyuan 100, Chaoyang District
Beijing 100124 (China)
e-mail: linyangcn@yeah.net