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EDITORIAL

Can blood pressure in the first trimester predict the development of gestational hypertensive disorders?

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This editorial refers to 'Blood pressure tracking during pregnancy and the risk of gestational hypertensive disorders. The Generation R Study'†, by R. Gaillard *et al.*, on page 3088

Hypertensive disorders in pregnancy remain a major cause of maternal, fetal, and neonatal morbidity and mortality worldwide. Pregnant women with hypertension are at higher risk for severe complications such as abruption placentae, cerebrovascular accidents, organ failure, and disseminated intravascular coagulation. The fetus is at risk for intrauterine growth retardation, prematurity, and intrauterine death.

Hypertension is the most common medical problem in pregnancy, accounting for approximately a quarter of all antenatal admissions. The definition of hypertension in pregnancy was not uniform for a long time;[1,2] it used to be defined as an elevation in blood pressure during the second trimester from a baseline reading in the first trimester or from pre-pregnancy levels. However, a definition based on absolute blood pressure values (systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$90 mmHg) is now preferred. Hypertension in pregnancy is not a single entity but comprises (i) pre-existing hypertension; (ii) gestational hypertension with its subunit of (iii) pre-eclampsia; (iv) pre-existing hypertension with superimposed gestational hypertension with proteinuria; and (v) antenatally unclassifiable hypertension (*Table 1*).

Identification of the risk factors associated with gestational hypertension, and with pre-eclampsia in particular, would be of utmost importance. *Table 2* shows factors that can easily be measured at the first prenatal appointment and that increase the likelihood of pre-eclampsia in any pregnancy. Meads *et al.* reviewed 27 tests for prediction of pre-eclampsia.[3] However, only a few reached a specificity >90%, and no single test met the clinical standards for a predictive test.[4]

Gaillard *et al.* have examined, in a population-based cohort study of 8482 pregnant women, whether blood pressure in early pregnancy tracks to the third trimester and whether this tracking is influenced by maternal characteristics and is associated with the risk of gestational hypertensive disorders.[5] Blood pressure was measured in each trimester of pregnancy by the Omron HEM-907, a digital oscillometric device. Correlation coefficients between the first and third trimesters for systolic and diastolic blood pressure were 0.47 and 0.46, respectively. The odds ratio for staying in the highest strata from the first to third trimester for systolic blood pressure was 3.09 [95% confidence interval (CI) 2.73–3.50], and for diastolic blood pressure 3.28 (95% CI 2.90–3.69). Blood pressure tracking coefficients were lower in younger, shorter, and non-European women, and in women with higher gestational weight gain. Systolic and diastolic blood pressure changes from the second to third trimester, but not from the first to second trimester, were positively associated with the risks of pregnancy-induced hypertension and pre-eclampsia. The authors concluded that blood pressure tracks moderately during pregnancy and is influenced by maternal characteristics. The second-to-third trimester increases in systolic and diastolic blood pressure are associated with an increased risk of gestational hypertensive disorders.

Blood pressure measurement is a screening test that is used in antenatal care to detect or predict hypertensive disease.[6] Prediction of women at risk for developing gestational hypertension or pre-eclampsia is crucial to allocation of monitoring resources and, possibly, use of preventive treatment. With the banning of mercury sphygmomanometers in some European countries, automated oscillometric devices are being increasingly used. Automated blood pressure measuring devices have been shown to be unreliable in severe pre-eclampsia and tend to under-record the true value. It is imperative that only devices validated according to recognized protocols to determine their accuracy are used in

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Table 1 Classification of hypertension in pregnancy

1. Pre-existing hypertension; either preceding pregnancy or developing before 20 weeks gestation; usually persisting >42 days post-partum.
2. Gestational hypertension; developing after 20 weeks gestation and resolving, in most cases, within 42 days post-partum.
3. Pre-eclampsia; gestational hypertension with proteinuria >3 g/24 h.
4. Pre-existing hypertension plus superimposed gestational hypertension with proteinuria; pre-existing hypertension with further worsening of hypertension and protein excretion ≥3 g /day in 24 h urine collection after 20 weeks gestation.
5. Antenatally unclassifiable hypertension; if blood pressure was first recorded after 20 weeks gestation; reassessment is necessary at or after 42 days post-partum.

Table 2 Risk markers for pre-eclampsia at antenatal booking according to the pre-eclampsia community guidelines (PRECOG)[10]

	Unadjusted relative risks (95% CI)
Nulliparity	2.91 (1.28–6.61)
Multiparous women	
Pre-eclampsia in any previous pregnancy	7.19 (5.85–8.83)
10 years or more since last baby born	Increased[a]
Age 40 years or older	
Nulliparous women	1.68 (1.23–2.29)
Multiparous women	1.96 (1.34–2.87)
Body mass index ≥35 kg/m^2	1.55 (1.28–1.88)
Family history of pre-eclampsia (mother or sister)	2.90 (1.70–4.93)
Diastolic blood pressure of ≥ 80 mmHg at booking	Increased[a]
Proteinuria at booking appointment (≥+ on dipstick testing, on more than one occasion, or quantified at ≥300 mg/24 h)	Increased[a]
Multiple pregnancy	2.93 (2.04–4.21)
Underlying medical disorders	
Pre-existing hypertension	Increased[a]
Pre-existing renal disease	Increased[a]
Pre-existing diabetes	3.56 (2.54–4.99)
Presence of antiphospholipid antibodies	9.72 (4.34–21.75)

[a]Risk of pre-eclampsia increased but by how much is unknown.

pregnancy (see www.dableducational.org). The reported mean differences have been as great as 15 mmHg when compared with mercury sphygmomanometers, and 25 mmHg when compared with intra-arterial measurements. Unfortunately, to the best of our knowledge, the Omron HEM-907 device used in the Generation R Study by Gaillard *et al.* has not been validated for blood pressure measurement in pregnancy.[7]

Women with pregnancies leading to fetal death ($n = 72$) and induced abortion ($n = 27$) were excluded from the analysis. It is likely that the proportion of hypertensive pregnancies was particularly high among these two groups.

As in almost any study on hypertensive disorders of pregnancy, blood pressure levels before pregnancy were not available. It cannot be excluded that some of the women in this study may have had pre-existing hypertension masked by the physiological fall in blood pressure that occurs early in pregnancy, and are subsequently falsely labelled as having gestational hypertension when blood pressure levels return to or exceed the pre-pregnancy level in late pregnancy.

Poon and co-workers used the combination of maternal medical history and mean arterial pressure at 11^{+0} to 13^{+6} weeks gestation to predict pre-eclampsia and gestational hypertension and found that, for a 10% false-positive rate, 60% of those who will develop pre-eclampsia, and 40% of those who will develop gestational hypertension, can be identified.[8] One important predictor in their models, however, is a previous history of pre-eclampsia; prediction of pre-eclampsia has proven to be most difficult in nulliparous women. In a meta-analysis involving 34 studies and 60 599 women, mean arterial pressure was a better predictor of pre-eclampsia than systolic blood pressure, diastolic blood pressure, or an increase in blood pressure when blood pressure was measured in the first or second trimester of pregnancy.[9]

In the Generation R Study, systolic blood pressure, diastolic blood pressure, and mean arterial pressure tracked equally.

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However, diastolic blood pressure and mean arterial pressure were more strongly associated with the risks of pregnancy-induced hypertension and pre-eclampsia as compared with systolic blood pressure. Traditionally, the criteria used to define pre-eclampsia have lacked consistency and have overemphasized diastolic blood pressure. Diastolic-only thresholds are still recommended for diagnosis in the community in the UK;[10] this may be reasonable for pragmatic reasons to avoid confusion arising from multiple endpoints. On the other hand, intracranial haemorrhage in women with pre-eclampsia has been rising in the UK in recent years.[11] Life-threatening intracranial haemorrhage can occur despite only a modest increase in diastolic blood pressure, and a paradigm shift is needed toward considering antihypertensive therapy for severely pre-eclamptic and eclamptic patients when systolic blood pressure reaches or exceeds 155–160 mmHg. [12]

In conclusion, the study by Gaillard *et al.* has shown that blood pressure tracks moderately during pregnancy. From the point of view of statistical analysis, the study seems to be well conducted; however, no definition of blood pressure tertiles for the study population is provided, which could be possibly useful in clinical practice.

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