Daily serial hemodynamic data during pregnancy and seasonal variation: the BOSHI study

Short title: Hemodynamic data during pregnancy

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Declaration of Interest

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Abstract

Although there are some reports that low plasma volume or increased cardiac output is associated with developing preeclampsia, there are few reports of daily serial hemodynamic data during normal pregnancy. The aim of this study was to determine home heart rate (HR), double product (DP), and shock index (SI) changes during pregnancy using home blood pressure (BP) measurements. A total of 37,092 home BP and HR measurements were obtained from 425 normal pregnant women, attending a maternity hospital in Japan. A mixed linear model adjusting for meteorological data and gestational age was used for the analysis. HR and SI gradually increased by gestational week 32 and then decreased, while DP increased linearly during pregnancy. When the summer season was defined as June to September based on minimum outside temperature ≥15°C, the interaction for hemodynamic data between seasonality and minimum outside temperature was significant (all $p<0.0001$). Although SBP and DP were consistently and significantly correlated with daily minimum outside temperature, SI in summer was positively correlated with minimum outside temperature ($\beta=0.22$), but such relationship was weak in the remaining seasons ($\beta=0.084$). SI remained within a narrow range (0.68–0.70 bpm/mmHg) throughout a year, however, it peaked in summer (0.72–0.75 bpm/mmHg). The effect of seasonality was weaker than the effect of gestational age on HR and DP. During pregnancy, HR and SI peaked at gestational week 32. DP increased gradually as gestational age increased. Such data might be valuable for considering hemodynamic changes during pregnancy.

Key words: Clinical Science, Blood pressure measurement/monitoring, Pre-eclampsia/pregnancy, self-monitoring of blood pressure

Text

Introduction

Gestational hypertension and preeclampsia are common disorders during pregnancy, with the majority of cases developing at or near term (1). Plasma volume is significantly lower in preeclampsia than in normal pregnancy at a gestational age of 14–17 weeks (2). Recently, it has been reported that cardiac output is increased in the first trimester in women who develop preeclampsia (3, 4). Although hemodynamic changes during pregnancy appear to be important, there are few reports dealing with daily serial hemodynamic changes during pregnancy.

Heart rate (HR), double product (DP), which is calculated from systolic blood pressure (SBP) multiplied by HR, and shock index (SI), which is calculated from HR divided by SBP, are parameters that are easy to obtain from blood pressure (BP) measurements. DP is a surrogate measure of myocardial oxygen demand and cardiac workload, which has recently become widely used in cardiovascular medicine (5). SI is an index to determine hypovolemia, which is accompanied by hypotension and tachycardia (6, 7), and SI predicts the quantity of hemorrhage from a ruptured ectopic pregnancy better than HR or SBP alone (6). Birkhahn et al reported that acute blood loss of 450 mL significantly increased SI from 0.61 to 0.65 bpm/mmHg (7).

Although home BP measurement has been recognized as an important tool among pregnant women (8, 9), data derived from home BP measurements are rare. The guidelines for hypertension in pregnancy do not mention home BP measurements (10-12). We have previously reported the associations among home BP, gestational age, and seasonal variation (13). The aim of this study was to collect daily serial hemodynamic data (HR, DP, and SI) during pregnancy with adjustment for gestational age and seasonal variation using home measurements of BP and HR.

Methods

The present report is part of the Babies and their Parents' Longitudinal Observation in Suzuki Memorial Hospital on Intrauterine Period (BOSHI) study (13). The study was conducted at Suzuki Memorial Hospital, which is the only hospital specializing in obstetrics, gynecology, and in vitro fertilization in the Sendai City area of Miyagi Prefecture, Japan. Sendai is the central city of northeastern Japan. There were 1,098 births in Suzuki Memorial Hospital in 2006. All study protocols were approved by the Institutional Review Board of

Tohoku University School of Medicine and by the Hospital Review Board of Suzuki Memorial Hospital.

In Japan, the interval for medical check-ups during pregnancy is once every 4 weeks until week 23, once every two weeks until week 35, and once a week after 36 weeks.

Only healthy pregnant women before gestational week 20 with no history of hypertension and who could measure their home BP during pregnancy were included after obtaining their written informed consent. Gestational age was calculated by last menstrual period with correction for crown-lump length before 12 weeks of gestation. After delivery, the obstetrician and physician verified that the pregnancy had been normal without hypertension or proteinuria.

Subjects

A total of 3,362 women was diagnosed as being pregnant between October 1, 2006 and September 30, 2009 and reserved delivery in the hospital. All of these women were invited to participate by a poster and a letter from the investigating staff; 1032 women received an explanation of the research from a physician, pharmacist, or midwife.

Daily serial hemodynamic data using home BP measurements

Home BP was measured using an HEM-747IC or HEM-7080IC semiautomatic device (Omron Healthcare, Kyoto, Japan) based on the cuff-oscillometric method, which generates not only a digital display of both systolic BP (SBP) and diastolic BP (DBP) (14), but also heart rate (HR). DP was calculated from SBP multiplied by HR, and SI was calculated from HR divided by SBP.

Physicians, pharmacists, and midwives instructed subjects on how to perform home BP measurements. The subjects were asked to measure their home BP every morning within 1 h of waking, after micturition, before breakfast, while seated, and after resting for more than 1 min, based on the Japanese Society of Hypertension guidelines for self-monitoring of BP at home (15), and to keep recording their home BP until 1 month after delivery.

Meteorological data

Meteorological data measured at Sendai Meteorological Observatory for the period during which home BP measurements were taken included: daily minimum, maximum, and mean outside temperatures; daily mean atmospheric pressure, relative humidity, and duration of sunshine. Normalized data were also obtained from Sendai Meteorological Observatory, as averaged meteorological data from 1970 to 2000.

Statistical analysis

Daily serial hemodynamic data (SBP, HR, DP, and SI) were examined using a mixed linear model with gestational age as the fixed effect and subjects as the random effect. When we adjusted for seasonal effect, meteorological data were also regarded as fixed effect. We further examined yearly variation of daily serial hemodynamic data; we examined weekly serial hemodynamic data in a year without adjustment for meteorological data. The measurement week of the year was regarded as a fixed effect in a mixed model.

We analyzed data using the SAS package (version 9.2, SAS Institute Inc., Cary, North Carolina, USA). Values are expressed as mean ± SD and least square means were calculated by the mixed linear model and expressed as mean with their 95% confidence intervals (CI) (Figure 1, Figure 2).

A sample size of 387 women was required to estimate the distribution of mean home BP values within a ± 0.8 mmHg range at a 95% confidence interval (CI), assuming that the SD of home BP values in pregnant women is 8 mmHg based on the previous report (13).

Results

Subjects

A total of 518 women finally entered the study. Nine women were excluded due to fetal death in the first trimester. Another 4 women transferred to other hospitals because of threatened premature delivery (2 women), premature rupture of the membranes (1 woman), and diabetes (1 woman). One woman was excluded because she transferred to the nearest midwifery clinic. During the follow-up period, 51 women developed gestational hypertension or preeclampsia; they were excluded. Among the remaining 452 healthy pregnant women, home BP monitoring was not available for 27 women during pregnancy. Data of the remaining 425 healthy pregnant women were analyzed.

The mean age of the 425 healthy pregnant women analyzed in this study was 31.3±4.6 years at entry. Their mean height, weight and BMI were 158.4±5.3

cm, 54.2±9.0 kg, and 21.6±3.4 kg/m^2, respectively. The frequency of ever smokers was 16.8% and that of ever drinkers was 50.7%. Among them, 71% of ever smokers and 95% of ever drinkers stopped during pregnancy. The mean birth weight of their children was 3,054±394 g.

Daily serial hemodynamic data and gestational age

The association between SBP, HR, DP, and SI and gestational age using a mixed linear model without adjusting for meteorological data is shown in Fig. 1. HR and SI increased gradually, reaching peak values at gestational week 33, while DP increased linearly from the first trimester to the third trimester.

After adjusting for meteorological data, the associations between these daily hemodynamic data and gestational age showed the same tendency (data not shown).

Daily serial hemodynamic data and seasonal variation

The yearly variation in SBP, HR, DP, and SI calculated using a mixed linear model adjusting for gestational age is shown in Fig. 2. SBP decreased gradually from January to August and gradually increased from August to

December. HR decreased gradually from January to June, after which it increased and reached its peak value in August. DP was the highest in January and decreased to its lowest value in June. From June to December, DP increased gradually. Although SI was stable from January to June and from October to December, it increased from June to August, reached its peak in August, and then decreased to October.

When summer season was defined as June to September based on a minimum outside temperature ≥15°C, HR, DP, and SI showed significant inverse associations with the daily minimum outside temperature in summer as compared to the other seasons. SBP and DP were consistently and significantly correlated with daily minimum outside temperature throughout the year (summer: β (SBP) = −0.3055 and β (DP) = −0.2172, and in the other seasons: β (SBP) = −0.1999 and β (DP) = −0.2051, all p < 0.0001). The correlation between HR and daily minimum outside temperature were significant but weak in each season (summer: β=0.0095, in the other seasons: β=-0.0560, all p < 0.0001) While, SI was positively correlated with daily minimum outside temperature in summer (β = 0.2235), whereas, in the remaining seasons weak correlations were observed (β = 0.0811; P = <0.0001). The interactions between daily minimum outside temperature and seasonality (summer versus the other seasons) for SBP, HR, DP and SI were significant (Table 1, all interactions $p < 0.0001$).

Hemodynamic parameters, gestational age, and seasonal variation

The associations among hemodynamic parameters (SBP, HR, DP, and SI), gestational age, and seasonal variation are shown in Fig. 3. SBP increased gradually and achieved its peak values (≥110 mmHg) at gestational week 40. HR increased gradually and reached its peak (≥75 bpm) at gestational week 32. DP increased gradually as gestational age increased and reached its peak (≥8,000·mmHg·bpm) at gestational week 40. The effect of expected date of birth on HR and DP was smaller than the effect of gestational age. On the other hand, women who were to give birth in winter had a high SI (≥0.73 bpm/mmHg) in their first or second trimester, and women who were to give birth in autumn had a high SI (≥0.73 bpm/mmHg) in their third trimester.

Discussion

This is the first study to describe the relationships of HR, DP, and SI with a combination of gestational age and seasonality in a cohort of normal pregnant women. This study collected daily serial hemodynamic data during pregnancy on the basis of self-measurement of BP and HR at home.

Heart rate

As in a previous study that used ambulatory BP measurement (16), home HR showed the highest value in gestational week 32 in the present study. Seasonal variations exist in home BP values (17), however, there are few studies that have observed seasonal variation of HR. Some articles reported that there is no significant relationship between seasonality and HR (18, 19), while Izzo et al reported wintertime HR increased by 7% ($P < 0.017$), with larger parallel increases in systemic vascular resistance (+24%, $P < 0.0017$) and plasma norepinephrine (+26%, $P < 0.017$) (20). In the present study, the association between HR and temperature was weak, but the association was significant.

Double product

The DP of SBP and HR indicates cardiovascular load. DP is a surrogate measure of myocardial oxygen demand and cardiac workload, which has recently become widely used in cardiovascular medicine (5). There is a report using ambulatory BP monitoring that showed that DP increased from summer to winter (daytime) by 1,053 mmHg·bpm for smokers (21). In the present study, DP was also higher in winter than in summer. The interaction between seasonality and temperature on the effect on DP was significant.

Rang et al reported that cardiac output was higher in preeclampsia or gestational hypertension without fetal growth restriction but not in preeclampsia or gestational hypertension with fetal growth restriction (4). Recently, De Paco et al. reported that cardiac output between 11^{+0} and 13^{+6} weeks of gestation was increased in women who developed preeclampsia (3). In the present study, DP increased gradually as gestational age increased, and the effect of seasonality and expected date of birth on DP was less marked than that of gestational age. DP might be a good way of evaluating cardiac workload in pregnancy due to its linear association with gestational age.

Shock index

SI, which is calculated from HR divided by SBP, is an effective way to diagnose hemorrhagic shock following injury, which is accompanied with hypotension and tachycardia (6, 7). In the present study, women who were to give birth in winter had a high SI in their first or second trimester. Women who were to give birth in winter spent their first trimester or second trimester during the summer season. The first trimester SI of the women who were to give birth in winter was 0.72–0.77 bpm/mmHg, while the first trimester SI of the women who were to give birth in other seasons was 0.66–0.70 bpm/mmHg. Birkhahn et al. reported that acute blood loss of 450 mL significantly increased the SI from 0.61 to 0.65 bpm/mmHg (7). SI might also represent hypovolemia. Women who are to give birth in winter might have hypovolemia in their first to second trimester. Similarly, women who are to give birth in autumn might have hypovolemia in their last trimester.

Plasma volume in pregnancies complicated by preeclampsia is reported to be significantly lower than in normal pregnancies in the first trimester (2). In this study, plasma volume is reported to be the first parameter to show significant intergroup difference among the parameters of progesterone, aldosterone, estradiol and their combination. Although further studies are necessary to investigate which factors changed before and after hypovolemia, there might be some association between hypovolemia in the first trimester in summer and the incidence of preeclampsia in winter. SI might be a good marker of dehydration in summer, since a similar trend was observed for HR (Fig. 2).

Limitations

There are some limitations in this study. First, SI seems to be a good way to identify hypovolemia within one subject; however, it is impossible to compare SIs among individuals because the SI is low with high BP. Another method may be necessary to identify hypovolemia. There are no previous reports showing that SI reflects chronic hypovolemia, in the same way as acute hypovolemia. Further study is needed to evaluate the amplitude of hypovolemia in chronic conditions. Second, in our study, we did not perform echocardiography or electrocardiography; therefore, we cannot evaluate the real clinical meaning of the DP using such physiological examinations. Another approach might be necessary to evaluate the real clinical meaning of DP. Third, these data are limited to normotensive pregnant women, because we did not perform a similar analysis in preeclamptic women, since few subjects developed preeclampsia. Serial changes of indirect indices might be modified by hospitalization, medication, and termination in subjects with preeclampsia.

Conclusion

This study collected daily serial hemodynamic data during pregnancy using home BP monitoring. DP increased gradually as gestational age increased, and the effect of seasonality and expected date of birth on DP was less marked than that of gestational age. SI might be useful for identifying hypovolemia within individuals. Such data might be useful for examining hemodynamic changes during normal pregnancy, as well as identifying hemodynamic changes during abnormal pregnancy.

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