Effects of Interpregnancy Interval on Blood Pressure in Consecutive Pregnancies

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The lower risk of preeclampsia observed in parous women has prompted a hypothesis that cardiovascular adaptation from a first pregnancy has ongoing benefits which contribute to a reduced risk of preeclampsia in the second pregnancy. However, how the interpregnancy interval affects mean arterial pressure (MAP) as an indicator of cardiovascular adaptation in subsequent pregnancies has not been well studied. The authors examined the effect of interpregnancy interval on MAP in consecutive pregnancies using data from the Collaborative Perinatal Project (1959–1965) and a semiparametric random-effects regression model. Prenatal MAP measurements were available for 533 women with both first and second births. MAP was lower in the second pregnancy (by approximately 2 mmHg) for very short interpregnancy intervals. However, this difference diminished when the interval increased, and it totally disappeared for intervals longer than 2 years. The authors conclude that although MAP is lower in the second pregnancy than in the first pregnancy, the effect persists for only a short time. It is therefore unlikely that mechanisms involving MAP as an indicator of cardiovascular adaptation contribute appreciably to the reduced risk of preeclampsia in subsequent pregnancies. However, it does not rule out the possibility that other mechanisms of cardiovascular adaptation persist longer.

birth intervals; blood pressure; pre-eclampsia; pregnancy

Abbreviations: CPP, Collaborative Perinatal Project; MAP, mean arterial pressure.
reduction. Here we discuss whether MAP reduction as an indicator of vascular adaptation may explain the reduced risk of preeclampsia in multiparous women.

MATERIALS AND METHODS

The women included in the Collaborative Perinatal Project (CPP) received care at one of 12 large, urban US hospitals between 1959 and 1965 (13). Comprehensive socioeconomic, demographic, and behavioral information was obtained at enrollment through individual interviews. Overall, the CPP recruited approximately 60,000 women, of whom 7,994 had at least two of their pregnancies recorded prospectively during the study period (13). In the current study, the analysis was confined to women with singleton pregnancies for whom the first and second pregnancies were recorded \(n = 3,280\), who were recruited before 21 weeks of gestation during both pregnancies \(n = 1,251\), and for whom prepregnancy weight, height, and smoking behavior were reported for both pregnancies \(n = 883\). Because this study focused on normal physiologic effects, the sample was further restricted to women whose first pregnancies ended with full-term delivery (i.e., 37–43 weeks' gestation) and whose second pregnancy lasted at least 28 weeks \(n = 704\). Additionally, we excluded women with preexisting chronic hypertension in the first pregnancy \(n = 54\) or hypertensive disorders in the first pregnancy \(n = 117\). This resulted in a total of 533 women for the analysis.

For each participant, blood pressure was recorded at entry, at each prenatal visit, during labor and delivery, and postpartum. In the majority of these visits, blood pressure was measured twice. We averaged the two readings and report a single measurement. The analyses were restricted to the antepartum blood pressure measurements taken between days 70 and 280 of pregnancy, as determined by the start of the last menstrual period. No intrapartum blood pressure was used. The systolic and diastolic measurements were converted to MAP using the formula (14): MAP = 1/3 systolic blood pressure + 2/3 diastolic blood pressure.

The interpregnancy interval between the two pregnancies was estimated as the difference between the last menstrual period in the second pregnancy and the date of delivery in the first pregnancy. Given that the CPP lasted only 6 years, the maximum duration of the interpregnancy interval was 5 years. Body mass index was calculated as self-reported prepregnancy weight (in kilograms) divided by the square of height measured at enrollment (in meters). To assess maternal smoking at entry, the women were asked to report the average number of cigarettes they currently smoked per day. Paternity change between the two pregnancies was not recorded explicitly but was evaluated on the basis of paternal age (matching the difference in paternal age and the difference in maternal age between the two pregnancies) and change in the marital status of the mother. Paternity was classified as changed, unchanged, or uncertain (whether it changed).

Statistical analysis

We first examined the blood pressure trajectory during the course of each pregnancy (primiparas and multiparas, respectively). Since nonlinear changes in MAP were expected (14–19), a spline regression model was used to allow for a flexible form of the trajectory while controlling for correlation within measurements in the same woman (function fitting generalized additive mixed models \(gamm\) as implemented in the \texttt{mgcv} library in \texttt{R} software (20)). For a given parity, a joint regression trajectory was specified. At the same time, each woman was permitted to have an individual intercept (i.e., the difference in her blood pressure in relation to the average blood pressure for the sample at each time point).

To examine the association between interpregnancy interval and MAP reduction in the second pregnancy, we restricted the data to MAP obtained after 139 days of gestation. The 140th day of gestation was selected as a cutoff because all women included in the sample had contributed blood pressure measurements by then. For comparison of MAP in both pregnancies, the midpoint of the MAP trajectory after 139 days in each pregnancy was selected. This corresponded to the 240th day in both pregnancies. The individual MAP was calculated as a woman’s average MAP within the study population on that day plus her individual (random) effect using a separate \textit{gamm} model (described above) in each pregnancy. Estimates from both pregnancies were subtracted to obtain the individual MAP difference for each woman. Finally, a semiparametric regression model with locally weighted regression \(lowess\) or \textit{loess} (21) was employed to investigate the association between interpregnancy interval and difference in MAP between pregnancies. We repeated the analysis for all 3,280 women with first and second pregnancies recorded in the CPP data set to assess the sensitivity of our analysis towards exclusion criteria. Given a potential difference between races with regard to MAP (16), we performed a separate analysis for non-Hispanic Whites. We also studied the effects of the interval on the postpartum blood pressure in the subsample of women with first and second pregnancies recorded in CPP for whom postpartum MAP in both pregnancies was available \(n = 629\).

RESULTS

Our study population was generally young and had normal body weight. Approximately 40 percent smoked during pregnancy (table 1). Seventy-two percent of the participants were White. Paternity in the two pregnancies was unchanged in 81 percent of women, changed in 4 percent, and uncertain in 15 percent. Most women had a relatively short interpregnancy interval of 1 year or less, reflecting the lack of effective contraceptive methods and a desire to have more children during the study period. An interpregnancy interval longer than 3 years was uncommon (only 4 percent) (figure 1).

Figure 2 shows that the MAP followed a U-shaped trajectory in both pregnancies, with the average readings at the corresponding stages of gestation being consistently lower during the second pregnancy relative to the first pregnancy. Differences in MAP between pregnancies were slightly smaller during the first trimester and towards the end of
the pregnancy, indicating that MAP reduction is a phenomenon restricted to pregnancy.

In the final semiparametric regression model, only MAP in the first pregnancy and difference in body mass index between the two pregnancies were significantly associated with the difference in MAP (data not shown). After adjustment for these variables, MAP was approximately 2 mmHg lower in the second pregnancy among women with very short interpregnancy intervals (MAP2/MAP1: 1.78 mmHg (95 percent confidence interval: 3.02, 0.63) for an interval of 1 month and 1.10 mmHg (95 percent confidence interval: 1.65, 0.45) for an interval of 6 months) (figure 3). The difference diminished linearly as the length of the interval increased, and it totally disappeared for intervals longer than 2 years (MAP2/MAP1: 0.12 mmHg (95 percent confidence interval: 0.78, 1.02) for an interval of 2 years).

These findings were similar for women who were younger than 24 years of age at first pregnancy and women who were aged 24 years or more at first pregnancy (data not shown), and the findings persisted when the sample was restricted to non-Hispanic Whites. Other variables investigated in the model—smoking behavior (in the second pregnancy and its change between pregnancies), body mass index (in the second pregnancy), maternal age in the second pregnancy, paternity change, socioeconomic status, and race/ethnicity—were not associated with MAP changes between pregnancies. The results were similar for the total sample of all women with first and second pregnancies included in the CPP (n = 3,280; data not shown). The postpartum MAPs did not differ after the first and second pregnancies (for MAP2 − MAP1, mean = 0.76 mmHg (standard deviation, 11.1); p = 0.09), nor did interpregnancy interval have any significant effect on postpartum MAP (data not shown). Both are consistent with the observation that MAP difference between pregnancies diminishes towards the end of gestation.

**DISCUSSION**

We examined changes in MAP during women’s first and second pregnancies and the effects of interpregnancy interval on these changes in the second pregnancy. Consistent with previous studies (14–19), we found a decline in MAP in the second trimester which was greater during the second pregnancy than during the first pregnancy. However, the extra decline in the second pregnancy diminished with

![Figure 1. Distribution of interpregnancy intervals in the study population (n = 533), Collaborative Perinatal Project, United States, 1959–1965.](https://academic.oup.com/aje/article-abstract/168/4/422/105872)

![Figure 2. Trajectories of mean arterial pressure (MAP) in the first and second pregnancies, Collaborative Perinatal Project, United States, 1959–1965. The solid line shows data for the first pregnancy, and the dashed line shows data for the second (with accompanying 95% confidence intervals).](https://academic.oup.com/aje/article-abstract/168/4/422/105872)
MAP was proposed as one of the indicators of cardiovascular adaptation in pregnancy, and better cardiovascular adaptation is thought to be a mechanism explaining a reduced risk of preeclampsia in parous women (10, 12). However, the short interval observed for the reduction in MAP is inconsistent with epidemiologic findings on the association between interpregnancy interval and risk of preeclampsia. Conde-Agudelo et al. (4) showed that the risk of preeclampsia in parous women with a short interpregnancy interval was approximately half of that in nulliparous women, but it returned to the levels of nulliparous women after an interpregnancy interval of 6 years. Basso et al. (3) reported a linear increase in risk of preeclampsia with increasing interpregnancy intervals between 2 and 7 years, but the risk was still lower than that in the first pregnancy at 7 years. Skjæerven et al. (5) found that even 10 years after the previous pregnancy, multiparous women still had a lower risk of preeclampsia than the nulliparous women. Therefore, the findings for MAP do not explain the association between interpregnancy interval and risk of preeclampsia in multiparous women.

The major strength of our study was the large sample, given the challenges of collecting data on consecutive pregnancies. However, several limitations should be noted. First, we relied on routine clinical measurement of blood pressure. Errors in blood pressure measurement in our study were more likely to have been random than systematic, and they were probably independent of interpregnancy interval and parity. This would have resulted in larger variance and wider confidence intervals, but the point estimate—the difference in MAP between the first and second pregnancies—was probably unaffected. Second, since our study included only women with relatively short interpregnancy intervals, we were unable to study the effects of intervals longer than 3 years; however, it is unlikely that after 3 years the protective effects of the first pregnancy would reemerge. Third, a higher percentage of women in our study were smokers in comparison with contemporary society. We investigated the effect of smoking in the first pregnancy and changes in smoking between pregnancies. None of these variables significantly affected our results.

We opted to restrict our sample to a small fraction of those who were originally enrolled, for the purpose of obtaining a homogenous sample for assessment of the physiologic effect of interpregnancy interval on MAP. As demonstrated in the sensitivity analysis, the results in the restricted sample were similar to those for the total sample. Still, our results might not be generalizable to, for example, women with hypertensive disorders. Previous studies have indicated that the blood pressure trajectory for women with hypertensive disorders differs from that for normotensive women (14, 15, 24). While these women were included in the reanalysis of the total sample, the number was too small to warrant a separate analysis. The results were not affected by the inclusion, but this might have resulted from too small a sample rather than from the effects’ being similar.

We included assessment of paternity change in our analysis. There is ongoing controversy as to whether paternal change contributes to an increased risk of preeclampsia as the interpregnancy interval increases (3, 5, 8, 9). We did not

FIGURE 3. Mean effect of interpregnancy interval on the difference in mean arterial pressure (MAP) between the first and second pregnancies (MAP2 – MAP1) for a theoretical woman with an average MAP (83.5 mmHg) in the first pregnancy and no difference in body mass index between pregnancies. Collaborative Perinatal Project, United States, 1959–1965. Analysis of the association between interpregnancy interval and difference in MAP was restricted to intervals of 3 years or less, because for longer intervals the data were very sparse (4% of the women were excluded). Dashed lines, 95% confidence interval.

increasing interpregnancy intervals and disappeared altogether after 2 years.

It remains unclear why MAP decline in the second pregnancy is greater than that in the first. Clapp et al. (11) speculated that a biologic memory of the cardiovascular system might contribute to a deeper decline in blood pressure in the second pregnancy, but they did not specify possible mechanisms. Khong et al. (22) observed an increase in the proportion of the nonmuscular component in the wall of the uterine spiral arteries with parity. Recent data showing lower levels of anti-angiogenic factors in the second pregnancy than in the first also provide a plausible mechanism for the deeper MAP decline in the second pregnancy (23). However, in none of these studies were findings correlated with the interpregnancy interval.

To the best of our knowledge, the impact of interpregnancy interval on a reduction in MAP was previously assessed only in one small study (12). When Bernstein et al. (12) fitted a simple linear regression model to the data of 47 women, they found a lower MAP in the second pregnancy than in the first pregnancy when the interpregnancy interval was less than 3 years but a higher MAP when the interval was longer. However, the authors did postulate that the effect of previous pregnancy is likely to disappear over time in a nonlinear fashion (12). Our finding confirms their speculation. Nonetheless, both their study and ours indicate that the impact of interpregnancy interval on blood pressure in the second pregnancy is short-lived (<2–3 years).
find an effect of paternal change on MAP, but this has to be qualified by the fact that we used a crude and error-prone assessment of paternal change.

In summary, MAP is generally lower in the second pregnancy than in the first pregnancy. However, this difference disappears after only 2 years. The duration of the impact of a previous pregnancy on MAP in the subsequent pregnancy appears to be too short for this mechanism to explain the observed reduced risk of pre-eclampsia in the second pregnancy. While MAP is one of the indicators of cardiovascular adaptation in pregnancy, we cannot rule out the possibility that other mechanisms of cardiovascular adaptation which are not reflected in MAP contribute to the reduced risk of preeclampsia in parous women.

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REFERENCES