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Effect of Pregnancy Interval on Second Pregnancy Blood Pressure Following Prior Preeclampsia

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Abstract

Objective: Preeclampsia generally occurs in first pregnancies and tends not to recur when the interpregnancy interval (IPI) is short. We hypothesized that, in women experiencing preeclampsia in their first pregnancy, the difference in mean arterial pressure (MAP) across pregnancy between their index and subsequent pregnancy would be inversely associated with the length of time between pregnancies and that the interval between pregnancies will be directly associated with the likelihood of preeclampsia recurrence. **Methods:** This was a retrospective chart review evaluating 171 women diagnosed with preeclampsia during their first pregnancy who had a subsequent pregnancy at our institution. Blood pressures were collected from each pregnancy, marking the recurrence of hypertensive disorders, including preeclampsia. Antepartum MAP was compared between pregnancies, examining differences as a function of IPI. **Results:** There was a significant association of IPI with the reduction in MAP between pregnancies across trimesters ($P = .04$), but this reduction became smaller over time. The MAP during the third trimester decreased significantly between pregnancies across all patient groups (IPI <24 months: −5.7 mm Hg, $P < .0001$; IPI 24-48 months: −4.5 mm Hg, $P < .0001$; IPI >48 months −3.4 mm Hg, $P = .03$). The recurrence rate of preeclampsia did not vary significantly with IPI ($P = .21$). **Conclusion:** The IPI influences the MAP of the second pregnancy in women with prior preeclampsia. Shorter IPI is associated with a greater reduction in MAP when compared to the longer IPI. Although there was a trend toward higher preeclampsia recurrence with longer IPI, this trend did not reach statistical significance.

Keywords

preeclampsia, interpregnancy interval, hypertension

Introduction

Pregnancy is a physiologic state during which the maternal cardiovascular system undergoes significant adaptation to support the growing fetal–placental unit.[1] Major physiologic changes occurring in early pregnancy include primary reduction in peripheral vascular resistance and a significant increase in plasma volume.[2] These changes are associated with important maternal cardiovascular system remodeling that serves to accommodate the increase in intravascular volume. These adaptations result in increased arterial compliance and initially a reduced blood pressure (BP). Previously, we and others have demonstrated that reductions in mean arterial blood pressure (MAP) can also be identified in the postpartum period, when compared to prepregnancy measurements,[3] and reduced MAP has been observed in pregnancies that follow uncomplicated term deliveries when compared to BP during the first pregnancies. This reduction in MAP has been noted to be strongly associated with the interval between pregnancies, with the MAP returning to prepregnancy levels as the interpregnancy interval (IPI) grows longer.[4-6]

Preeclampsia, a disorder characterized by new onset of hypertension with proteinuria and/or end-organ injury, has been proposed to be associated with limited ability of the prepregnancy maternal vasculature of some individuals to adapt to pregnancy-associated volume expansion.[7] Specifically, some women who develop preeclampsia may have a prepregnancy cardiovascular phenotype that limits their ability to remodel in response to the physiologic volume expansion that is necessary for healthy pregnancy outcomes.[8] Preeclampsia most commonly occurs during a woman's first pregnancy and is less likely to recur in subsequent

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pregnancies when the IPI is short.[9-11] We propose that the protective effect of reduced IPI is due to the influence of the cardiovascular remodeling that occurs during pregnancy and persists postpartum, resulting in a transient increase in vascular compliance and an associated protective effect on the maternal cardiovascular system entering future pregnancy.[6] While we and others have demonstrated that this effect occurs with uncomplicated pregnancy, we believe that this response to pregnancy may be an important contributor to the IPI-dependent risk for the recurrence of preeclampsia.

In this study, our hypothesis is that the length of time between pregnancies is inversely associated with MAP throughout subsequent pregnancy and positively correlated with the likelihood of recurrence of preeclampsia.

Materials and Methods

Identification of Research Participants

This study was a retrospective chart review using existing medical records. All research was approved by the University of Vermont Institutional Review Board, Committee on Human Research in Medical Sciences. OBNet, a registry used by the University of Vermont Medical Center (UVMMC), was used to identify candidate patients. Each patient chart was subsequently reviewed to confirm diagnoses and collect antepartum, intrapartum, and immediate postpartum information. Medical records of the women who had been diagnosed with preeclampsia at UVMMC during their first pregnancy between 1995 and 2014 were reviewed. Participants were included if they were nulliparous before the index preeclamptic pregnancy and had a second subsequent delivery at UVMMC. All patients had BP readings across at least 2 trimesters of each pregnancy. Trimesters were defined as first (weeks 1-12 + 6 of gestation), second (weeks 13-25 + 6 of gestation), and third (weeks $\geq$26 of pregnancy). Patients with thrombophilic disease, fetal anomalies, or pregnancy associated with multiple gestations were excluded from this study. If external medical records were needed for review of early pregnancy BP assessments, the outside institutions were contacted and permission to collect data from their medical records was obtained.

Data Collection

Once patients were identified, data were collected from their medical records and stored in a password-protected data sheet accessible to the research team. Clinical data that could impact BP and risk of preeclampsia were recorded to evaluate for potential confounding factors including age, race, educational level, smoking status, as well as prepregnancy weight, body mass index (BMI), weight gain during pregnancy, number of prenatal visits, and medications used during each pregnancy. Participants were required to have BP assessments spanning at least 2 trimesters to be considered for inclusion. History of chronic hypertension and antihypertensive medication usage was documented. The gravidity and parity of each participant were noted. In addition, newborn birth weight, gestational age, birth date and time, and Apgar scores at 1 and 5 minutes postpartum were recorded.

For each pregnancy, a maximum of 25 antepartum BP readings were collected for each patient. Blood pressures were also recorded up to 3 days postpartum. If more than 1 BP reading was taken per day, a mean systolic and mean diastolic BP value was calculated. These BPs were acquired through either manual or automated devices in the clinical environment and consistent with clinical standards. The MAP was calculated by using the formula: ([2 $\times$ diastolic BP] + systolic BP)/3. Each patient was categorized as diagnosed with preeclampsia without severe features, preeclampsia with severe features, or hemolysis, elevated liver functions, and a low platelet count (HELLP) syndrome. Preeclampsia was defined by new-onset hypertension, according to the 2013 American College of Obstetrics and Gynecology criteria, accompanied by proteinuria or evidence of other end-organ effects.[12] The HELLP syndrome is defined by hemolysis, elevated liver functions, and a low platelet count. In the case of second pregnancies, the diagnosis of gestational hypertension, the development of hypertension during pregnancy, was also documented.

The study participants were segregated into 3 groups depending on their IPI. The IPI was divided as follows: <24 months (IPI < 24), 24 to 48 months (IPI 24-48), and >48 months (IPI > 48). The IPI was defined as the time between deliveries.

Statistical Analysis

The clinical and demographic characteristics of the first and subsequent pregnancies were compared using paired *t* tests and McNemar tests for continuous and categorical measures, respectively. Differences in MAP, systolic pressure, and diastolic pressure between the first and subsequent pregnancies were analyzed using repeated-measures analyses of variance (ANOVAs). The model included 2 within-participant factors, pregnancy (initial/subsequent), trimester (first, second, third), and 1 across-participant factor IPI (<24 months, 24-48 months, >48 months), and their interactions. Other comparisons of continuous and categorical outcomes across the 3 groups defined by the length of IPI were done using 1-way ANOVAs and χ^2 tests, respectively. All statistical analyses were performed using SAS Statistical Software version 9.3 (SAS Institute, Cary, North Carolina). Statistical significance was determined based on $P < .05$.

Results

Clinical and Demographic Characteristics

Index and subsequent pregnancies of 171 patients were included in the analyses. When grouped according to IPI, 40 patients had an IPI of <24 months, 105 patients had an IPI of 24 to 48 months, and 26 patients had an IPI of >48 months. The

Table 1. Clinical and Demographic Characteristics of Pregnancies.[a]

Characteristic	Pregnancy 1	Pregnancy 2	*P*
Age (years)	27.9 (5.7)	30.7 (5.6)	<.001
Prepregnancy weight (kg)	76.3 (22.1)	79.3 (24.3)	<.001
Weight gain (kg)	16.5 (7.6)	14.2 (7.3)	<.001
Gestational age at delivery (weeks)	36.4 (3.5)	38.1 (2.1)	<.001
Apgar at 1 minute	6.9 (2.0)	7.7 (1.7)	<.001
Apgar at 5 minutes	8.3 (1.6)	8.8 (1.1)	.003
Birth weight (g)	2823 (959)	3276 (72)	<.001

[a]All data are expressed as mean (standard deviation). Significance is based on paired *t* tests.

Table 2. Differences in Clinical Characteristics in the Pregnancies.[a]

Characteristic	Pregnancy 1 (%)	Pregnancy 2 (%)	*P*
Tobacco use	14.0	10.5	.083
CHTN	16.9	22.7	.002
MFM patient	17.4	26.2	.004
Preterm delivery	30.2	15.1	<.001
BW <1500 g	11.6	2.3	<.001
BW <2500 g	11.5	2.5	.005
Preeclampsia	60.5	14.0	<.001
Preeclampsia (severe)	39.5	8.7	<.001
Preeclampsia (any)	100.0	22.7	<.001
HELLP	15.1	2.3	<.001

Abbreviations: BW, birth weight; CHTN, chronic hypertension; HELLP, hemolysis, elevated liver functions, and a low platelet count; MFM, maternal fetal medicine.

[a]For first and second pregnancies, percentage of participants in each category is shown. The *P* values for the differences between the 2 pregnancies are stated for each category. Significance is based on McNemar test.

majority of patients were Caucasian, 97% (166/171), consistent with regional distribution. All patients had appropriate pregnancy dating, based on, or consistent with, an early ultrasound examination. Five of the index pregnancies resulted in an intrauterine fetal demise. Two of the subsequent pregnancies had the same outcome. There were 33 patients with at least 1 abortion (either spontaneous or elective) between the index and subsequent pregnancies.

Clinical and demographic characteristics of the pregnancies are outlined in Table 1. Table 2 depicts the differences in various clinical characteristics between the 2 pregnancies and the significance of these differences. Maternal age, prepregnancy weight, and the diagnosis of chronic hypertension were all significantly more common, and there was a trend toward less maternal smoking, in second pregnancies. All of these factors would favor higher BP in second pregnancies compared to the first. Tobacco use, chronic hypertension, use of medication (including antihypertensive medication), and prepregnancy weight were not significantly different across the patients with different IPI. In general, trends favoring an increased risk of hypertension in second pregnancies included higher maternal age, higher prepregnancy weight, greater gestational ages at delivery, and reduced tobacco use.

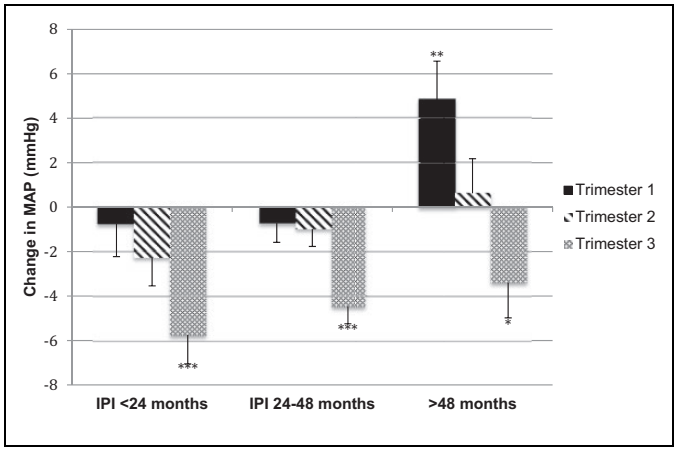

Figure 1. Interpregnancy interval versus change in mean arterial pressure (MAP): For each trimester, the changes in MAP between first and second pregnancies are displayed for each group. ***$P < .001$, **$P < .01$, *$P < .05$. Significance is based on analyses of variance.

Mean Arterial Pressure and IPI

Overall, there was evidence of a significant association of IPI with the difference in MAP between pregnancies when BP measurement was combined within pregnancies and examined across the entire pregnancy (ANOVA, $P = .04$). When the second pregnancy was considered as a whole, rather than as individual trimesters, with direct comparison to first pregnancies, there was a significant decrease in the MAP between first and second pregnancies when the IPI was <24 months (-2.92 ± 0.92 mm Hg; $P = .0018$) and 24 to 48 months (-2.06 ± 0.56 mm Hg; $P = .0003$). The change in MAP between pregnancies was nonsignificant when IPI was >48 months (-0.68 ± 1.13 mm Hg; $P = .55$). Systolic and diastolic BPs were significantly and similarly reduced in the second pregnancies of the same patient groups (systolic: IPI <24 months: -3.77 ± 1.24 mm Hg, $P = .003$, IPI 24-48 months: -2.99 ± 0.75 mm Hg, $P = .0001$; diastolic: IPI <24 months -2.5 ± 0.89 mm Hg, $P = .006$, IPI 24-48 months: -1.59 ± 0.54 mm Hg, $P = .004$).

The change in MAP across each trimester of pregnancy was compared among the groups (Figure 1). There was a significant decrease in MAP during the third trimester between the first and second pregnancies in all 3 of the IPI patient groups examined. These reductions demonstrated diminishing differences with movement toward first pregnancy values with greater IPI (IPI <24 months: -5.7 mm Hg, $P < .0001$; IPI 24-48 months: -4.5 mmHg, $P < .0001$; IPI >48 months -3.4 mm Hg, $P = .03$). Also observed was a significant increase in BP in the first trimester when the IPI was $\geq$48 months.

Examining postpartum BPs, we observed a significant reduction in MAP on the first day postpartum of the second pregnancy in all 3 of the patient groups when compared to the first day postpartum of the index pregnancy. Patients with an IPI of <24 months had an average reduction of 6.0 mmHg, and patients with IPI of 24 to 48 months and >48 months had an average reduction of 6.7 and 6.5 mm Hg, respectively (IPI <24 months, $P = .001$; IPI 24-48 months, $P < .0001$; IPI >48

Table 3. Diagnoses in First and Second Pregnancies.[a]

Pregnancy	Gestational Hypertension	Preeclampsia	Preeclampsia (Severe)	HELLP
1	–	104	68	26
2	26	24	15	4

Abbreviation: HELLP, hemolysis, elevated liver functions, and a low platelet count.
[a]Number of patients diagnosed with gestational hypertension, preeclampsia, severe preeclampsia, and HELLP in first and second pregnancies. Patients with HELLP syndrome are also classified as having severe preeclampsia.

months, $P = .004$). The differences in MAP on the first day postpartum between the first and second pregnancies were not significantly correlated with IPI ($P = .95$).

Preeclampsia Recurrence

In the second pregnancies, 38% (65/171) of the patients experienced a hypertensive disorder, either preeclampsia or gestational hypertension. There were 39 (23%) patients who experienced recurrent preeclampsia in their second pregnancy (Table 3). It was observed that, although nonsignificant, there was a higher frequency of preeclampsia recurrence in the second pregnancies with longer IPI. When the IPI was <24 months, 12.5% of patients were diagnosed with preeclampsia in the second pregnancy (either with or without severe features), while 25.7% and 26.9% of patients experienced recurrence when the IPI was 24 to 48 months and >48 months, respectively ($P = .21$). This same trend was observed when examining recurrence of any hypertensive disorder of pregnancy.

Among the subset of women with preterm preeclampsia in their first pregnancy (n = 52), we observed recurrence of preeclampsia in 14 (27%) of 52 patients and recurrence of any form of hypertensive disease within pregnancy in 20 (38%) of 52 patients. Recurrence rates among those with term disease in their first pregnancies was 25 (21%) of 119 for preeclampsia and 45 (38%) of 119 for any form of pregnancy-associated hypertension. These differences were not significant.

Of interest, 63% (42 of 68) of women who exhibited severe features of preeclampsia in the first pregnancy experienced a normal, uncomplicated second pregnancy. Sixty-two percent (64/104) of women who exhibited preeclampsia without severe features in the first pregnancy experienced a normal, uncomplicated second pregnancy.

Discussion

Overall, when first and subsequent pregnancies were each considered as a whole, rather than as individual trimesters, there was a significant reduction in BP differences as the interval between the pregnancies lengthened. This suggests that when a first pregnancy is complicated with preeclampsia, there is a persistent effect on the maternal cardiovascular system that appears to enhance vascular compliance. This effect appears to extend for years postpartum paralleling observations that have been made following uncomplicated pregnancies.[5,13] The third-trimester MAP of the second pregnancy was found to be significantly decreased in all 3 patient groups compared with the index pregnancy. This was expected due to the fact that there was a selection bias for high BP in the first pregnancies and the majority of cases of preeclampsia are diagnosed during the third trimester of pregnancy.[14] Additionally, when the extent of changes in MAP was compared directly among the different IPI patient groups, the differences between the patient groups were significant. Specifically, patients with an IPI of <24 months and 24 to 48 months had a significantly greater reduction in MAP across pregnancies than patients who experienced an IPI of >48 months, suggesting that this effect wanes over time. Clinically, this implies that women diagnosed with preeclampsia during their first pregnancy may have a greater probability of a subsequent nonhypertensive pregnancy if the IPI is short. Our data demonstrated a trend in this direction that is supported by other observation.[9-11] Of interest, the observations made in the current study are noted despite second pregnancies which have significantly more underlying risk factors for hypertension in pregnancy identified, including more chronic hypertension, greater BMI prepregnancy, and a trend toward reduced cigarette smoking (Tables 1 and 2). We also recognize that the relatively small number of patients with an IPI greater than 48 months in our cohort is likely to have reduced our ability to identify whether longer IPIs might also have a persistent effect on BP in subsequent pregnancies.

An apparent outlier to our overall observations was the identification of a significant increase in first-trimester BP when the IPI was greater than or equal to 48 months. This difference results primarily from the low BP observed within the first trimester of the first pregnancy for these women as highlighted in Figure 2 rather than an elevation of BP within the first trimester of the second pregnancies. The first-trimester BP differences across the IPI groups were not, by themselves, significantly different.

It has been demonstrated that following a normal pregnancy, the reduction in MAP during subsequent pregnancy diminishes as the interval between pregnancies increases. In a prior study, by our group, we observed that the changes in third-trimester BPs between the first and second pregnancies approached 0 when the IPI reached approximately 4 years.[4] Another study, employing a large cohort of women, suggested that the MAP returned to the nulliparous baseline, during the course of subsequent pregnancy, after only 2 to 3 years.[5] Unlike the present study, both of these studies looked at women who had experienced an uncomplicated, normotensive first pregnancy. When we evaluated women who were diagnosed with preeclampsia during their first pregnancy, the MAP within the third trimester of the second pregnancy did not approach primiparous levels, even at an IPI of greater than 2 years. However, as the time interval between pregnancies grew longer, the MAP across all trimesters of the second pregnancies

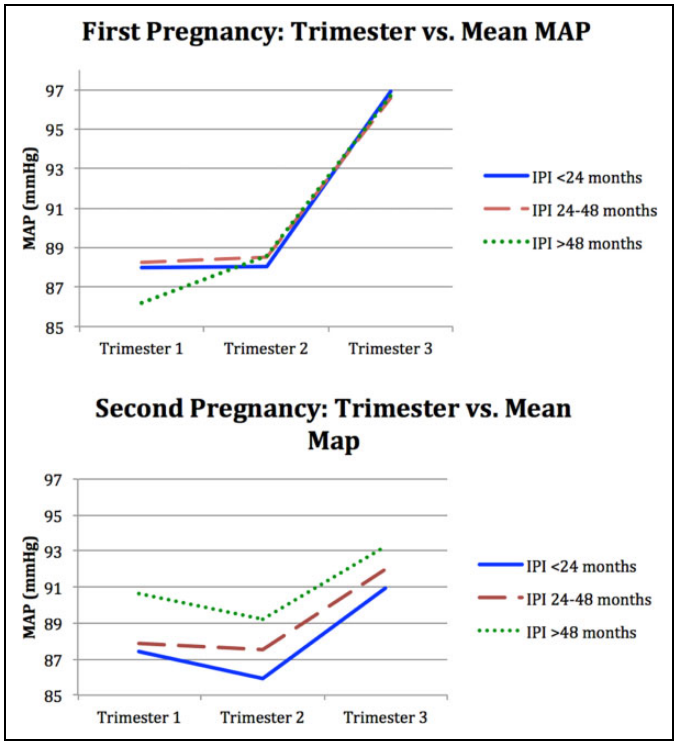

Figure 2. Mean arterial pressure (MAP) and interpregnancy interval (IPI). (Top) Trends in first pregnancy MAP for each group of patients, segregated by IPI. There was no significant difference in the MAP of any trimester between the 3 groups. (Bottom) Trends in second pregnancy MAP for each group of patients, segregated by IPI.

was observed to increase consistently, approaching levels observed in the first preeclamptic pregnancy. Of note, these BP observations, during the first pregnancy, were made predominantly prior to the diagnosis being established. It was also evident that the trends in BP changed when the first and second pregnancies were compared. As shown in Figure 2, in the first pregnancies, which were complicated by preeclampsia, the MAPs of the second trimester were approximately equal to those of the first trimester, demonstrating no evidence of the second-trimester reductions commonly associated with uncomplicated pregnancies. In the third trimester, MAP was noted to spike consistent with the onset of clinical preeclampsia. Overall, the second pregnancies demonstrate a trend that is similar to the BPs changes observed within a healthy pregnancy with the characteristic second-trimester nadirs.[13]

Mikolajczyk et al argued that because the MAP returns to baseline so rapidly following the first uncomplicated pregnancy, a reduction in MAP, and its implications regarding vascular remodeling, cannot underlie the lack of uniform recurrence of preeclampsia in second pregnancies.[5] This claim was supported with evidence that demonstrated that the degree and duration of MAP reduction did not correlate with the increasing probability of preeclampsia reccurence as suggested in epidemiologic studies.[9,10] Our results suggest, rather, that women who were diagnosed with preeclampsia in their first pregnancy may not follow the same physiological time line with regard to return to BP baseline as women who had a healthy first pregnancy. It has been observed that the risk of preeclampsia in second pregnancies approximately equals that of nulliparous women when the IPI is 10 years or greater.[9] Unfortunately, we did not have any patients in the current study who had an IPI nearing 10 years. Nevertheless, the regression of BP differences between pregnancies as a function of interval matches this epidemiologic evidence. Our data identify a reduction in the observed decrease in third-trimester BP of approximately 1.1 mm Hg for each 2-year observation window, beginning with a reduction of 5.7 mm Hg for recurrent deliveries within 2 years of the index preeclamptic pregnancy (Figure 2). If this pattern continued to project linearly, we would identify a return to baseline risk for each of the individuals within our cohort at approximately 10 years.

In this study, the overall recurrence rate of preeclampsia was 23%, which was in agreement with recurrence rate found in existing literature.[12,14,15] When recurrence was compared among women who exhibited severe features of preeclampsia or preterm disease in the first pregnancy with those who did not exhibit such symptoms, the percentage of normal, uncomplicated second pregnancies was not significantly different.

Due to the nature of a retrospective chart review, this study has its limitations. No control group was available for comparison, although we have previously published observations in a cohort of women with uncomplicated pregnancies.[4] In addition, a portion of the patients in the current analysis had early pregnancy losses (either spontaneous or elective) between the pregnancies of interest. The effect of these losses on subsequent pregnancy outcome was not independently analyzed. In measuring BP, multiple devices were employed within both the inpatient and multiple outpatient settings. The data on the specific measurement devices employed when the BP was obtained electronically and the potential change in those units over time were not available for the current analysis. Additionally, some of our cohort likely received low-dose aspirin in their second pregnancies, and this could be suspected of having some effect on reducing the BP observations in the second pregnancy. This possible effect was not independently analyzed. This influence, however, would only be expected to be a significant contributor in 10% to 15% of our population, and we had no evidence that the use of low-dose aspirin was differently represented in the different IPI groups.[16]

We have hypothesized that the nonuniform recurrence rate of preeclampsia is due to the cardiovascular modifications and vascular remodeling that occur during first pregnancies, protecting the maternal system from high BPs in subsequent pregnancies, even when the first pregnancy is complicated by preeclampsia. Although we found no significant difference in the rate of recurrence as the IPI increased from <24 to >48 months, there was a consistent increasing trend of recurrence in preeclampsia with a longer IPI. We hypothesize that the inclusion of longer IPI would result in clearer associations of IPI with BP changes and preeclampsia recurrence.

The role of new paternity has been identified as a risk factor for preeclampsia in parous women.[17] By extension, new

paternity in a second pregnancy could be playing a role in the differences in BP noted between pregnancies, interacting with the influence of IPI. In the current study, data on paternity were not available.

In conclusion, our data suggest that the interval between pregnancies does have an influence on the changes in MAP in subsequent pregnancies in women who were previously diagnosed with preeclampsia in their first pregnancies. With longer IPIs, there was a smaller degree of MAP change between the index preeclamptic pregnancies and the subsequent pregnancies. Although the IPI was not significantly associated with the recurrence of preeclampsia, we hypothesize that there would be a more conclusive result if additional data were collected on larger numbers of patients with IPIs approaching 10 years or greater. Overall, we believe this evidence supports a transient impact of pregnancy on cardiovascular compliance that could contribute to the recurrence risk of preeclampsia and help explain the lack of uniform recurrence and the association of increased IPI with greater recurrence rates.

Declaration of Conflicting Interests

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