2015

Evaluating the effect of preeclampsia and time interval on subsequent pregnancies blood pressure

https://hdl.handle.net/2144/16007

Boston University
EVALUATING THE EFFECT OF PREECLAMPSIA AND TIME INTERVAL ON
SUBSEQUENT PREGNANCIES BLOOD PRESSURE

by

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B.S., Boston College, 2013

Submitted in partial fulfillment of the
requirements for the degree of
Master of Science

2015
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I would like to dedicate this work to my parents, Billie and Gregory Howe. Without their constant and overwhelming support, none of my success would be possible.
ACKNOWLEDGMENTS

I would like to thank Dr. Ira Bernstein, Dr. Erica Hammer, and Mrs. Carole McBride for their help and guidance throughout my thesis project, as well as all the opportunities they have presented to me in the process.
EVALUATING THE EFFECT OF PREECLAMPSIA AND TIME INTERVAL ON
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LINDSAY HOWE

ABSTRACT

Introduction

Preeclampsia, a hypertensive disorder of pregnancy, affects 3% to 7% of
women throughout the world. Preeclampsia is a leading cause of maternal and
infant mortality worldwide, occurring primarily in nulliparous women. Despite
extensive research over the past decade, the underlying pathophysiological
mechanisms of the disease are largely unknown. A recent hypothesis has
suggested that when a pregnancy is complicated by preeclampsia, it is the result
of an inability of the maternal cardiovascular system to fully adapt to the
physiologic challenge of pregnancy. This may result when there is an underlying
and predisposing prepregnancy maternal cardiovascular state that leads to the
pathophysiologic consequences of preeclampsia when pregnancy is
superimposed.

Despite evidence for familial predisposition and presumed multifactorial
genetic inheritance, preeclampsia generally occurs in first pregnancies and does
not recur when the interpregnancy interval is short. One explanation for these
observations is that pregnancy itself modifies the maternal cardiovascular system
in ways that persist postpartum and reduce the risk for preeclampsia recurrence,
at least for a limited period of time. It has been demonstrated that the maternal
cardiovascular system is remodeled during pregnancy, and these changes extend postpartum. The long lasting reduction in mean arterial pressure postpartum that pregnancy induces, and the cardiovascular remodeling that accounts for this, may allow for easier adaptation to volume expansion in subsequent pregnancies, even when the first pregnancy was complicated by preeclampsia. As the maternal cardiovascular system returns, over time, to the baseline condition, this protective effect diminishes. With this knowledge, we hypothesize that the length of time between pregnancies is negatively correlated to the likelihood of recurrence of preeclampsia, and more narrowly that the length of time between pregnancies is inversely associated with mean arterial pressure differences comparing pregnancies across all trimesters.

**Methods**

This study was a retrospective chart review of existing medical records. We reviewed medical records of women who had been diagnosed with preeclampsia at Fletcher Allen Health Care, during their first advanced pregnancy between 1995 and 2014, who went on to have a subsequent pregnancy within that time period. We aimed to identify factors that could affect the blood pressure and risk of preeclampsia in women who were previously diagnosed, including previous medical history and demographic variables. We collected blood pressures from each pregnancy, across each trimester, marking the recurrence of preeclampsia and other complications. Mean antepartum mean
arterial blood pressure, pulse pressure, and systolic and diastolic blood pressures were calculated and compared between pregnancies examining differences as a function of interpregnancy interval.

Results

One hundred and seventy two subjects were identified for review. Overall, there was evidence of a significant association of interpregnancy interval (IPI) and the difference in mean arterial pressure (MAP) between pregnancies (p=0.04). The mean MAP of pregnancy decreased significantly between first and second pregnancies when the interpregnancy interval was <24 months (p=0.0018) and 24-48 months (p=0.0003), but the change was non-significant at interpregnancy intervals of >48 months (p=0.55). The mean MAP during the third trimester, specifically, decreased significantly between first and second pregnancies across all subject groups (IPI <24 months: p<0.0001; IPI 24-48 months: p<0.0001; IPI >48 months: p=0.03). Preeclampsia recurred in 39 of the second pregnancies. The recurrence rate of preeclampsia did not vary significantly with interpregnancy interval (p=0.21).

Discussion/Conclusions

The interval between preeclamptic pregnancies and subsequent pregnancies has an influence on the MAP of the second pregnancy. There is good evidence of a temporal influence, in that the shorter interpregnancy
intervals resulted in a greater reduction in MAP when compared to the longer interpregnancy interval. We believe that with additional research on interpregnancy intervals >48 months, there could be more a conclusive association identified between the rate of recurrence of preeclampsia and the length of interpregnancy interval.
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LIST OF ABBREVIATIONS

APGAR ................................ Appearance, Pulse, Grimace, Activity, and Respiration
BMI .......................................................... Body Mass Index
BW .............................................................. Body Weight
CHTN ....................................................... Chronic Hypertension
FAHC ...................................................... Fletcher Allen Health Care
GH ........................................................... Gestational Hypertension
IPI ............................................................. Interpregnancy Interval
MAP ........................................................ Mean Arterial Pressure
MFM ......................................................... Maternal-Fetal Medicine
PEC .......................................................... Preeclampsia
PPD1 ......................................................... First Day Postpartum
INTRODUCTION

Pregnancy, a physiologic “stress test of life” (Williams, 2003), requires the maternal body to adapt to significant demanding physiologic changes. The adaptive limitations of this maternal response are challenged in every pregnancy, and in some individuals, an inability to fully adapt to the physiologic challenge represented by gestation may lead to pathophysiologic consequences. We believe that preeclampsia, a disorder characterized by the new onset of hypertension and end organ injury, and a major contributor to perinatal and maternal mortality, is a disease that results from a limited ability of the maternal organism to adapt to pregnancy, specifically the physiologic volume expansion that is required for healthy pregnancy outcomes. Preeclampsia is defined by new-onset hypertension, and is often accompanied by proteinuria (the excretion of 300 mg or more of protein in a 24 hour period) or evidence of other end organ effects (Table 1). Hypertension is defined by a systolic blood pressure of ≥140 mm Hg, or a diastolic of ≥90 mm Hg. Severe preeclampsia, diagnosed by systolic blood pressure of ≥160 mm Hg or a diastolic blood pressure of ≥110 mm Hg, is primarily observed in first pregnancies (American College of Obstetricians and Gynecologists & American College of Obstetricians and Gynecologists, 2013; Barton & Sibai, 2008). The incidence of preeclampsia is approximately 3% to 7% in the general population (Basso et al., 2001). Due to lifestyle changes, and medical advances (i.e. increased obesity and assisted reproduction) as well as increased maternal ages, all of which are positively associated with disease, the
rates of severe preeclampsia rose 322% between 1980 and 2010 (Ananth et al., 2013). Unfortunately, knowledge of this disease remains limited, and more research will be necessary to understand its etiology and thereby decrease the damaging impact that preeclampsia has on women, children, and families worldwide.
Table 1: Diagnostic Criteria of Preeclampsia: Diagnostic criteria as determined by the American College of Obstetrics and Gynecology. This figure was taken from Hypertension in Pregnancy guidelines by ACOG (American College of Obstetricians and Gynecologists & American College of Obstetricians and Gynecologists, 2013).

<table>
<thead>
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| Blood Pressure                 | - Greater than or equal to 140 mm Hg systolic or greater than or equal to 90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure  
- Greater than or equal to 160 mm Hg systolic or greater than or equal to 110 mm Hg diastolic, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy |
| Proteinuria                    | - Greater than or equal to 300 mg per 24-hour urine collection (or this amount extrapolated from a timed collection)  
- Protein/creatinine ratio greater than or equal to 0.3*  
- Dipstick reading of 1+ (used only if other quantitative methods not available)  
Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following: |
| Thrombocytopenia               | - Platelet count less than 100,000/microliter                            |
| Renal insufficiency            | - Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease |
| Impaired liver function         | - Elevated blood concentrations of liver transaminases to twice normal concentration |
| Pulmonary edema                |                                                                        |
| Cerebral or visual symptoms    |                                                                        |

*Each measured as mg/dL.
Physiological manifestations of preeclampsia frequently include increased vascular resistance and reduced plasma volume, which are associated with the hypertension (Hale et al., 2010). Preeclampsia can present in a variety of unique ways and the severity and symptoms vary between women. About one quarter of women diagnosed with preeclampsia develop HELLP syndrome, defined by hemolysis, elevated liver functions, and a low platelet count. Other preeclamptic women do not develop any symptoms until after parturition (Osol & Bernstein, n.d.). Preeclampsia can progress to eclampsia, which is defined by the new onset of seizures, and can lead to stroke and ultimately death for both the mother and fetus. Most cases of preeclampsia occur in nulliparous women (women without prior pregnancies beyond 20 weeks) near term, but approximately 10% of cases occur before 34 weeks of gestation (van Rijn et al., 2006). If the fetus survives the pregnancy, serious fetal complications can occur as a result of preeclampsia including growth restriction, preterm delivery, placental abruption and ultimately, significant neonatal morbidity and developmental delays (Barton & Sibai, 2008). Adding to the overall uncertainty and ambiguity, the fundamental pathophysiologic mechanism of preeclampsia remains largely unknown (Bernstein et al., 1998).

There are a number of factors thought to increase the risk of preeclampsia including prepregnancy hypertension (including chronic hypertension), obesity (associated with insulin resistance), change of partner between pregnancies, a long interpregnancy interval, diabetes mellitus, increased maternal age, the use of assisted reproduction technologies, and pregnancies resulting in multiple
gestation (Barton & Sibai, 2008; Lynch et al., 2002; “Preeclampsia and High Blood Pressure During Pregnancy - ACOG,” n.d.). Although these risk factors have been established, there is no proven dependable method of predicting preeclampsia. Current predicative tests for preeclampsia include uterine artery waveform analysis and uterine notching in early or mid pregnancy employing ultrasound imaging, but these prognostic indicators have proven to have relatively low predictive values (Hale et al., 2010).

Women who receive the diagnosis of preeclampsia are often administered magnesium sulfate to protect them from developing seizures, as well as antihypertensive medication to combat the increases in blood pressure (Abad et al., 2015; Barton & Sibai, 2008). There is no current treatment for preeclampsia except this symptomatic management or delivery when the disease is deemed to represent an imminent maternal risk. Despite efforts to prolong pregnancy, worsening disease often requires preterm (>37 weeks gestation) delivery when disease presents prior to term gestation (“Preeclampsia and High Blood Pressure During Pregnancy - ACOG,” n.d.).

Intolerance to Volume Expansion

Over the past decade, extensive research has been conducted to investigate the numerous pathophysiologic abnormalities of preeclampsia and to attempt to determine potential etiologies. Women with chronic hypertension have a 25% incidence of preeclampsia. Woman with severe chronic hypertension have an incidence that approaches 50% (Barton & Sibai, 2008). Women who develop
Preeclampsia have been found to have increased arterial stiffness, as observed by an increased pre-pregnancy pulse pressure and pulse wave velocity (Hale et al., 2010; Hausvater et al., 2012). This increased arterial stiffness could result in a maternal cardiovascular system that is intolerant to the volume expansion required by pregnancy, leading to clinical hypertension (Bernstein et al., 1998). This hypothesis is supported by evidence of an increased risk of preeclampsia with multiple gestation, which requires a greater degree of volume expansion in comparison to singleton pregnancies (Lynch et al., 2002). Further support is offered by a decrease in incidence of preeclampsia in smokers. Smoking reduces the degree of expansion of plasma volume, protecting the maternal cardiovascular system from preeclampsia (Bruinse et al., 1985). Increased arterial stiffness not only potentially complicates a pregnancy, but it is also a known risk of heart failure, stroke, and coronary heart disease later in life (Hale et al., 2013). These are long-term outcomes that have been linked to the development of preeclampsia during pregnancy (Bushnell & Chireau, 2011; Mannisto et al., 2013; “Preeclampsia and High Blood Pressure During Pregnancy - ACOG,” n.d.). It has been demonstrated that women diagnosed with severe preeclampsia are more likely to develop cardiovascular disease at an earlier age than women diagnosed with preeclampsia without severe features (Osol & Bernstein, n.d.)

Even during uncomplicated first pregnancies, there is the suggestion that the maternal vascular system is stressed by the physiologic volume expansion. The majority of primigravidas, women in their first pregnancy, demonstrate an
increase of at least 20 mm Hg in diastolic blood pressure by the third trimester, while this rise in blood pressure is much less common in subsequent pregnancies. This suggests that even with an uncomplicated pregnancy, the ability to control blood pressure is challenged, and that the physiologic ability to manage plasma volume changes is enhanced in multiparous women (MacGillivray et al., 1969).

One mechanism that limits the increase in intravascular pressure is the endothelial response to shear stress (Koller et al. 1993). When the endothelial cells are exposed to increases in shear stress, they produce vasoactive substances, such as nitric oxide. These substances work to increase vessel diameter, protecting the maternal cardiovascular system from an increase in blood pressure (Chambers et al., 2001; López-Jaramillo et al., 2001). In preeclamptic conditions, this mechanism appears inadequate, unable to fully compensate for the significantly elevated intraluminal pressures, resulting in endothelial damage (Chambers et al., 2001).

**Vascular Remodeling and Recurrence**

Despite evidence for familial predisposition and presumed multifactorial genetic inheritance, preeclampsia generally occurs in first pregnancies and does not recur when interpregnancy interval is short (Ward & Lindheimer, 2009). This may result from pregnancy associated cardiovascular remodeling. It has been found that the cardiovascular remodeling that occurs during pregnancy extends postpartum. Due to these cardiovascular adaptations, there is a significant
decrease in mean arterial pressure (MAP), as well as pulse wave velocity, from pre-pregnancy to postpartum, in woman who experience a term pregnancy (Hale et al., 2013; Morris et al., 2015). Examining the relationship of blood pressure in uncomplicated first pregnancies compared with subsequent normal pregnancies within individual women, we and others observed that blood pressure was lower, across all trimesters in subsequent pregnancies. This reduction in MAP was found to diminish with time (Mikolajczyk et al., 2008; Bernstein et al. 2005). The interval of time between pregnancies, therefore, is negatively correlated to the difference in MAP between pregnancies. Additionally, Clapp and Capeless discovered there is increased cardiac output, as well as a decrease in peripheral resistance, maintained through one year postpartum when compared to measures obtained prior to pregnancy (Clapp & Capeless, 1997).

It is believed that the cardiovascular remodeling that occurs during pregnancy and which persists postpartum might facilitate the accommodation of increased plasma volume, protecting the maternal cardiovascular system in future pregnancies. While preeclampsia occurs during approximately 3.9% of first pregnancies, it occurs in only approximately 1.7% of subsequent pregnancies (Skjaerven et al., 2002). In general, the incidence of recurrence of the disease is between 5% and 25%, depending on the severity, and gestational age at onset, of the disease in previous pregnancies (McDonald et al., 2009; van Rijn et al., 2006). In the cases where preeclampsia did recur, it is typically less severe and the pregnancies often progressed without significant maternal or fetal complication (McDonald et al., 2009).
The risk of recurrence is directly correlated to the interval between pregnancies. The odds ratio for preeclampsia recurrence was found to be 1.16 per additional year between pregnancies. If the inter-birth interval was 10 years or longer, the risk of preeclampsia is approximately that of nulliparous women (Skjaerven et al., 2002). This increase in risk with time is related to MAP. Wright et al. demonstrated that MAP increases significantly with inter-pregnancy interval (Wright et al., 2015). This evidence suggests that the protective effect of preceding pregnancies against preeclampsia is only transient, and that MAP and the maternal cardiovascular system returns to baseline after a certain interval of time (Skjaerven et al., 2002).

While we have demonstrated that second pregnancies are associated with reduced blood pressure when compared to uncomplicated first pregnancies as a function of the time between conceptions, we have not examined the same phenomenon and, if present, its associated time frame, when those first pregnancies are complicated by preeclampsia. While there are numerous theories about preeclampsia and its fundamental mechanisms, little attention has been paid to the mechanism underlying its lack of uniform recurrence in subsequent pregnancies. By studying women who have been previously diagnosed with preeclampsia and following them throughout subsequent pregnancies, we hope to shed light on the fundamental pathophysiology of preeclampsia.
The Present Study

It has been shown that the maternal cardiovascular system is remodeled during pregnancy, and these changes extend postpartum. The persistent decrease in mean arterial pressure postpartum may identify a cardiovascular system that allows for easier adaptation to volume expansion in subsequent pregnancies, even if the first pregnancy was complicated by preeclampsia (i.e. increased vascular compliance). However as the maternal cardiovascular system returns to the baseline condition over time, this protective effect diminishes. With this knowledge, we hypothesize that the length of time between pregnancies is negatively correlated to the likelihood of recurrence of preeclampsia, and more narrowly that the length of time between pregnancies is inversely associated with mean arterial pressure differences comparing pregnancies across all trimesters.

Specific Aims

In order to evaluate the effect of time interval on changes in MAP and recurrence rate of preeclampsia, we will:

(1) Examine the association of the time interval between pregnancies and the change in mean arterial pressure, systolic blood pressure, diastolic blood pressure, and pulse pressure (an index of vascular stiffness) across all three trimesters of pregnancy.

(2) Examine the association of the time interval between pregnancies and the likelihood of recurrence of preeclampsia in subsequent pregnancies.
We expect that this study will show:

(1) The time interval between pregnancies will be inversely associated with the changes in MAP, systolic blood pressure, diastolic blood pressure, and pulse pressure in subsequent pregnancies in women who were previously diagnosed with preeclampsia

(2) The time interval between pregnancies will be inversely associated with the recurrence rate of preeclampsia.
METHODS

Identification of Research Subjects

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. In order to retrieve relevant medical records, we used OBNet, a registry used by Fletcher Allen Health Care (FAHC) to collect information concerning births at FAHC and at hospitals in the surrounding regions. We reviewed medical records of the women who had been diagnosed with preeclampsia at FAHC during their first pregnancy between 1995 and 2014. We restricted our research to women who were nulliparous before the pregnancy during which they were diagnosed. In addition, we only investigated subjects who had a second delivery at FAHC. It was required that all subjects had blood pressure readings across at least two 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 ≥26 of pregnancy) (Bernstein et al., 2005). Woman who had been previously diagnosed with thrombophilic disease, where fetal anomalies were identified or who had a pregnancy that resulted in multiple gestations, were excluded from this study.

In addition, there were two subjects that had been previously recruited for a separate clinical study conducted by at FAHC. Although they delivered their first born at an outside institution, where they were diagnosed with preeclampsia, their second deliveries were at FAHC. They matched all the inclusion criteria for
this study, so their pregnancy data was appropriate for inclusion in this study. If external medical records were needed for review, the outside institutions were contacted and permission to collect data from their medical records was requested.

**Data Collection**

Once the subjects were determined using the identifiers, we began to collect data from their medical records. We aimed to identify factors that could affect the blood pressure and risk of preeclampsia in woman who were previously diagnosed.

These factors included age, race, educational level, smoking status, pre-pregnancy weight and body mass index (BMI), total weight gained during the pregnancy, number of prenatal visits, medications used during pregnancy, and whether there were any spontaneous or therapeutic abortions between the two pregnancies of interest. If the subject had a history of chronic hypertension, antihypertensive medication, or if the patient was a Maternal-Fetal Medicine patient, this was documented. The gravidity, parity, and number of abortions (including spontaneous, therapeutic, or elective) of each subject were also noted. In addition, the newborn’s birth weight, gestational age, birth date and time, and Appearance, Pulse, Grimace, Activity, and Respiratory (APGAR) scores at one minute and five minutes postpartum were recorded (Appendix). For each pregnancy, a maximum of 25 antepartum blood pressure readings were collected for each subject. Blood pressures were also recorded up to three days
postpartum. If more than one blood pressure reading was taken per day, a mean systolic and mean diastolic blood pressure value was calculated. Each subject was noted as diagnosed with preeclampsia without severe features (PEC), or preeclampsia with severe features (PEC (severe)). It was also reported if the subject was diagnosed with HELLP in addition to severe preeclampsia. In the case of second pregnancies, diagnoses of gestational hypertension or no diagnosis were possibilities. All data was kept in a data sheet that was only accessible to the research team.

The study subjects were segregated into three groups depending on their interpregnancy interval. The interpregnancy interval (IPI) were divided as follows: <24 months (IPI <24), 24-48 months (IPI 24-48), and >48 months (IPI >48).

**Statistical Analysis**

The clinical and demographic characteristics of the first and subsequent pregnancies were compared using paired t-tests and McNemar’s tests for continuous and categorical measures, respectively. Differences in mean arterial pressure, systolic pressure, diastolic pressure, and pulse pressure between the first and subsequent pregnancies were analyzed using repeated measures analyses of variance. The model included two within-subject factors, pregnancy (initial/subsequent), trimester (1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd}), and one across-subject factor interpregnancy interval (<24 months, 24-48 months, > 48 months), and their interactions. Other comparisons of continuous and categorical outcomes across the three groups defined by length of interpregnancy interval were done using
one way analyses of variance and chi square tests, respectively. All statistical analyses were performed using SAS Statistical Software Version 9.3 (SAS Institute, Cary NC). Statistical significance was determined based on $p<.05$. 
RESULTS

Clinical and Demographic Characteristics

First and second pregnancies of 172 subjects were included in the analyses. When grouped according to interpregnancy intervals, 40 subjects had interpregnancy intervals of <24 months, 105 subjects had interpregnancy intervals of 24-48 months, and 26 subjects had interpregnancy intervals of >48 months. The majority of subjects were Caucasian, 97% (166/172), which is representative of the Vermont population. All subjects had appropriate pregnancy dating (consisting of an ultrasound before 20 weeks gestation). Five of the first pregnancies resulted in a fetal demise, while two of the second pregnancies had the same outcome. There were 33 subjects who had at least one abortion (either spontaneous or therapeutic) between the two pregnancies of interest.

Clinical and demographic characteristics of the pregnancies are outlined in Table 2. Table 3 depicts the differences in various clinical characteristics between the two pregnancies and the significance of these differences.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pregnancy 1 (%)</th>
<th>Pregnancy 2 (%)</th>
<th>P</th>
</tr>
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<tr>
<td>Tobacco Use</td>
<td>14.0</td>
<td>10.5</td>
<td>p = 0.083</td>
</tr>
<tr>
<td>CHTN</td>
<td>16.9</td>
<td>22.7</td>
<td>p = 0.002</td>
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<td>MFM Patient</td>
<td>17.4</td>
<td>26.2</td>
<td>p = 0.004</td>
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<td>Preterm Delivery</td>
<td>30.2</td>
<td>15.1</td>
<td>p &lt; 0.001</td>
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<tr>
<td>BW &lt; 1500 grams</td>
<td>11.6</td>
<td>2.3</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>BW &lt; 2500 grams</td>
<td>11.5</td>
<td>2.5</td>
<td>p = 0.005</td>
</tr>
<tr>
<td>PEC</td>
<td>60.5</td>
<td>14.0</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>PEC (severe)</td>
<td>39.5</td>
<td>8.7</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>PEC (any)</td>
<td>100.0</td>
<td>22.7</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>HELLP</td>
<td>15.1</td>
<td>2.3</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

**Table 3: Differences in Clinical Characteristics in the Pregnancies:** For first and second pregnancies, percentage of subjects in each category is shown. The p values for the differences between the two pregnancies are stated for each category. Significance is based on McNemar’s test. The “PEC (any)” category consists of all subjects who were diagnosed with preeclampsia, regardless of severity of features. CHTN = Chronic hypertension; BW= birth weight; MFM = Maternal Fetal Medicine.
When the subjects were compared with regard to their interpregnancy interval, the subjects who experienced interpregnancy intervals >48 months were significantly younger than subjects who experienced interpregnancy intervals of <24 months and 24-48 months (p=0.02; p=0.04). The mean age at the second pregnancy was not significantly different across the groups.

Tobacco use, chronic hypertension, use of medication (including antihypertensive medication), and prepregnancy weight were not significantly different across the subjects with different interpregnancy intervals.

Mean Arterial Pressure and Interpregnancy Interval

Overall, there was evidence of a significant association of inter-pregnancy interval and the difference in MAP between pregnancies (ANOVA, P=0.04). The change in MAP between the first and second pregnancies was also calculated for each group of subjects. When pregnancy was considered as a whole, rather than as individual trimesters, there was a significant decrease in the MAP between first and second pregnancy when the interpregnancy interval was <24 months (p=0.0018). The same was true when the interpregnancy interval was 24-48 months (p=0.0003). When the interpregnancy interval was >48 months, the overall change in MAP from first to second pregnancy was non-significant.

In addition to the overall change in MAP between first and second pregnancies, the change in MAP across each trimester of the pregnancies was compared among the groups (Figure 1). There was a significant decrease in
MAP during the third trimester between first and second pregnancies in all three of the subject groups examined.

Figure 1: Interpregnancy Interval vs. Change in MAP: For each trimester, the changes in MAP between first and second pregnancies are displayed for each group. “****” represents p<0.001, “***” represents p<0.01, and “**” represents p<0.05. Significance is based on analyses of variance.

When the changes in mean MAP across the pregnancies were compared, the degrees of change in subjects with interpregnancy intervals of <24 months and 24-48 months were significantly greater than those subjects with an interpregnancy interval >48 months (p = 0.01; p=0.03). This significance is manifested in the change across the first trimester (p=0.02; p=0.005). This data is depicted in Figure 2.
Upon examining postpartum blood pressures, we observed a significant reduction in MAP on postpartum day 1 (PPD1) in the second pregnancy in all three of the subject groups (IPI <24 months: p= 0.001; IPI 24-48 months: p<0.0001; IPI >48 months: p=0.004). The differences in MAP on (PPD1) between first and second pregnancies were not significantly correlated with interpregnancy interval (p=0.95).
Figure 2: MAP and Interpregnancy Interval: (Top) Trends in first pregnancy MAP for each group of subjects, segregated by interpregnancy interval. There was no significant difference in the MAP of any trimester between the three groups. (Bottom) Trends in second pregnancy MAP for each group of subjects, segregated by interpregnancy interval.

Systolic and Diastolic Blood Pressure and Interpregnancy Interval

When the three subject groups were compared, for an interpregnancy interval of <24 months, as well as for an interpregnancy interval of 24-48 months, the mean systolic blood pressure was significantly reduced between first and
second pregnancies (p=0.003; p=0.0001). Specifically, this significance is manifested in the third trimester for both subject groups (p<0.0001; p<0.0001). This significance does not carry over to subjects with an interpregnancy interval of >48 months.

The changes in diastolic blood pressure were also examined across the subject groups. When pregnancies were considered as a whole, rather than as individual trimesters, the mean diastolic blood pressure was significantly reduced in the second pregnancies compared to the first pregnancies when the interpregnancy intervals were <24 months and 24-48 months (p=0.006; p=0.004). This significance is due to the change in diastolic blood pressure during the second and third trimester when the interpregnancy intervals are <24 months (p=0.03; p=0.0003), and the third trimester only when the interpregnancy interval is 24-48 months (p<0.0001). When the interpregnancy interval is >48 months, the diastolic blood pressure is significantly higher in the first trimester, but significantly lower in the third trimester of the second pregnancies compared to the first pregnancies (p=0.001; p=0.03).

**Pulse Pressure and Interpregnancy Interval**

When all subjects groups were combined, the mean pulse pressures in the first and third trimesters were significantly lower in second pregnancies when compared to the first pregnancies (p=0.03; p=0.03). When third trimesters of the pregnancies were compared, the pulse pressure was significantly lower in the second pregnancy in subjects with an interpregnancy interval of <24 months, as
well as in subjects with an interpregnancy interval of 24-48 months (p=0.02; p=0.3). This significance did not carry over to subjects with an interpregnancy interval of >48 months.

Although the differences in mean antepartum pulse pressures between first and second pregnancies were not significantly different when the subject groups were compared, the difference in mean pulse pressure on the first day postpartum (PPD1) between pregnancies was associated with the length of time between pregnancies (p=0.002). When the interpregnancy interval was between 24-48 months, the mean pulse pressure on PPD1 was significantly lower in the second pregnancies when compared to that of the first pregnancies (p=0.02). When the interpregnancy interval is >48 months, the pulse pressure at PPD1 is significantly higher in the second pregnancies than the first pregnancies (p=0.01).

**Preeclampsia Recurrence**

It was required that all subjects be diagnosed with preeclampsia in their first pregnancy. In the second pregnancies, 38% (65/172) of the subjects experienced a hypertensive disorder, either preeclampsia or gestational hypertension. There were 39 subjects (23%) who experienced recurring preeclampsia in their second pregnancy (Table 4). Figure 3 depicts the first pregnancy diagnoses with the rate and severity of second pregnancy outcomes.
<table>
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<th>Pregnancy</th>
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<th>PEC</th>
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<th>HELLP</th>
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</table>

*Table 4: Diagnoses in First and Second Pregnancies:* Number of subjects diagnosed with gestational hypertension (GH), preeclampsia (PEC), severe preeclampsia, and HELLP in first and second pregnancies. Subjects with HELLP syndrome are also classified as having PEC (severe).
Figure 3: Initial Diagnosis and Second Pregnancy Outcomes:
First pregnancy diagnoses (in bolded boxes; top to bottom: preeclampsia without severe features, severe preeclampsia, and HELLP) along with the outcomes of the subsequent pregnancies. A diagnosis of gestational hypertension (GH) was possible during the second pregnancy. The number of subjects (n) and percentage of subjects were reported for each second pregnancy outcome.
It was observed that, although non-significant, there was a higher frequency of preeclampsia recurrence in the second pregnancies with longer interpregnancy interval. When the interpregnancy interval was <24 months, 12.5% of subjects were diagnosed with preeclampsia (either with or without severe symptoms) in the second pregnancy, while 25.7% and 26.9% of subjects experienced recurrence when the interpregnancy interval was 24-48 months and >48 months, respectively (p=0.21). The recurrence of severe preeclampsia, specifically, followed the same pattern in relation to interpregnancy interval (p=0.6).

Examining all hypertensive disorders complicating second pregnancies there were 15 of the 40 subjects (38%) with interpregnancy intervals of <24 months that experienced a recurrence of a hypertensive disorder (either preeclampsia or gestational hypertension). A hypertensive disorder occurred in the second pregnancies of 41 subjects (39%) and 9 subjects (35%) who experienced interpregnancy intervals of 24-48 months and >48 months, respectively.
DISCUSSION

Basic Characteristics and Interpregnancy Interval

Basic demographic and clinical characteristics can affect the risk of developing preeclampsia. For example, increased maternal age, obesity, and preexisting hypertension increases the risk of preeclampsia (Barton & Sibai, 2008; Bruinse et al., 1985). Tobacco use during pregnancy, on the other hand, has the opposite effect (Ananth et al., 2013). In the present study, differences in these basic characteristics were analyzed both across the two pregnancies and across the three subject groups. When the first and subsequent pregnancies were compared, the percent of tobacco use among the study population did not change significantly. As a result, tobacco use could not account for the decrease in mean arterial pressure observed in second pregnancies. There were, however, significantly more subjects with preexisting chronic hypertension, as well as more subjects that were patients of Maternal-Fetal Medicine during the second pregnancy. It can be theorized that a number of subjects were diagnosed with chronic hypertension following their first pregnancy, due to the persistent elevated blood pressures experienced during their postpartum period. It was expected that there would be more Maternal-Fetal Medicine patients during the second pregnancies. Although the rate of recurrence of preeclampsia is lower in multiparous women than nulliparous women, women who have had preeclampsia in the past are often monitored closely in their subsequent pregnancies to detect and manage complications. In the second pregnancies,
there were also significantly less preterm births and newborns with what we categorized as low birth weight (below 1500 grams) and very low birth weight (below 2500 grams). This was expected, since preeclampsia often results in both fetal growth restriction as well as iatrogenic preterm delivery soon after onset of the disease (Barton & Sibai, 2008; “Preeclampsia and High Blood Pressure During Pregnancy - ACOG,” n.d.).

When the three subject groups were compared, tobacco use, maternal prepregnancy weight, and rate of chronic hypertension across the three interpregnancy intervals were not significantly different. This suggests that any differences that were observed in the cardiovascular function of the women, as well as any differences in the rate of recurrence of preeclampsia, across the subject groups were not a result of these variables.

The mean maternal age at the time of first pregnancy was significantly younger in subjects with pregnancies >48 months apart when compared to the shorter interpregnancy intervals. Not surprisingly, this significance disappeared at the time of the second pregnancies. Due to the fact that the age at the time of second pregnancy was approximately the same across subject groups, any differences that were observed during the second pregnancies across the subject groups could not be a result of the maternal age. Our data indicates that the women who experienced an interpregnancy interval of >48 months did not have significantly more cases of severe preeclampsia or HELLP in their first pregnancy. If that were the case, these women might have been more cautious about conceiving a second time, causing them to wait longer in between
pregnancies. It can be theorized, however, that the younger women did not feel the need to conceive soon after their first pregnancy, even if they desired to become pregnant in the future. It is widely known that with advanced maternal age, the risk of adverse outcomes, such as chromosomal abnormalities, preterm birth, and preeclampsia in pregnancy increase and reductions in fertility are observed (Ananth et al., 2013; Bayrampour et al., 2012). The older women, those who experienced interpregnancy intervals of <24 months and 24-48 months, having already experienced a complicated pregnancy, may have been more inclined to conceive soon after their first pregnancy in order to avoid the risks associated with advanced maternal age. Regardless of the confounding reason, the age at the time of second pregnancy was approximately the same across the different interpregnancy intervals. Maternal age, therefore, could not account for differences seen between the subject groups.

Mean Arterial Pressure and Interpregnancy Interval

The maternal cardiovascular system is challenged during pregnancy, largely due to a significant increase in plasma volume. This can result in an increase in blood pressure across all three trimesters of pregnancy, even in uncomplicated pregnancies (Bernstein et al., 2005). It has been found that women who undergo normal, uncomplicated pregnancies routinely have lower MAP throughout the second pregnancy when compared to the first and that this reduction in MAP is a function of the interval between pregnancies (Bernstein et al., 2005; Mikolajczyk et al., 2008). In this study, we examined whether this trend
held true when the first pregnancy was complicated by preeclampsia. In addition to MAP, we examined the changes in systolic blood pressure, diastolic blood pressure, and pulse pressure across the pregnancies. The change in MAP across the third trimesters of all three subject groups was significant. This was expected due to the fact that there was a selection bias for high blood pressure in the first pregnancies, and the majority of cases of preeclampsia are diagnosed during the third trimester of pregnancy (van Rijn et al., 2006). Interestingly, we observed a significant increase in MAP overall when comparing MAP across pregnancy as a function of interpregnancy interval. These differences were specifically identified within the first trimester between first and second pregnancies in subjects with an interpregnancy interval of >48 months. Of note in this study, this range (>48 months) of interpregnancy interval was underrepresented in relation to the shorter interpregnancy intervals and we may have been underpowered to identify differences and trends in blood pressure across all trimesters that were specific to this interpregnancy interval. Further research would be useful to clarify the relationship of longer interpregnancy intervals with difference in blood pressure before a conclusion for the specific association is made.

When each pregnancy was considered as a whole, rather than individual trimesters, and compared directly to each other, the reduction in MAP between the two pregnancies was only significant with interpregnancy intervals of <24 months and 24-48 months. When the interpregnancy interval was >48 months, the change in MAP between the two pregnancies was not significant. This
evidence suggests that even when the first pregnancy is preeclamptic, there is a protective effect on the maternal cardiovascular system that extends postpartum. Additionally, when the degree of changes in MAP were compared among the subject groups, the differences between the subject groups were significant. Specifically, subjects with interpregnancy interval of <24 months and 24-48 months had a significantly greater reduction in MAP across pregnancies than subjects who experienced an interpregnancy interval of >48 months. Due to the fact that the mean MAP of the first pregnancies were not significantly different when the groups were compared, these differences in the degree of change in MAP must be due to the MAP in the second pregnancies.

It has been demonstrated that following a healthy pregnancy, the reduction in MAP diminishes as the interval between pregnancies increases. Bernstein et al. found that the changes in third trimester blood pressures between first and second pregnancies approached zero when the interpregnancy interval reached four to five years (Bernstein et al., 2005). Another study, using a large cohort of women suggested that the MAP returned to the nulliparous baseline after only two to three years (Mikolajczyk et al., 2008). Unlike the present study, both of these studies looked at women who had experienced an uncomplicated, non-preeclamptic first pregnancy. When we observed woman who were diagnosed with preeclampsia during their first pregnancy, the mean MAP of the second pregnancy did not approach nulliparous levels even at the longest interpregnancy interval. However, as the time interval between pregnancies grew longer, the MAP across all trimesters of the second
pregnancies were observed to increase consistently. It was also evident that the trends in blood pressure changed when first and second pregnancies were compared. As shown in Figure 2, in the first pregnancies, which were complicated by preeclampsia, the mean arterial pressures of the second trimester were approximately equal to those of the first trimester, demonstrating no evidence of the second trimester reductions found in normal pregnancies. In the third trimester, MAP was noted to spike consistent with the onset of clinical preeclampsia. The second pregnancies show a trend that is much more similar to the blood pressures of a healthy pregnancy. In normal pregnancies, the blood pressure tends to decrease between first and second trimesters, and increase between second and third trimesters (Hermida et al., 2000). The second pregnancies closely mimicked this trend, suggesting that the second pregnancies are much more representative of normal pregnancies than they are preeclamptic pregnancies.

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 can not underlie the lack of uniform recurrence of preeclampsia in second pregnancies as the time frames do not match. After studying our results, we suggest, rather, that women who were diagnosed with preeclampsia in their first pregnancy do not follow the same physiological timeline as women who had a healthy first pregnancy. It has been demonstrated that the risk of preeclampsia in second pregnancies approximately equals that of nulliparous women when the interpregnancy interval is ten years or
greater (Skjaerven et al., 2002). Unfortunately, we did not have any subjects in the current study that had interpregnancy intervals nearing 10 years. Further research must be done in order to conclude if the increased risk of preeclampsia ten years postpartum is associated with mean arterial pressures that approach baseline, nulliparous values.

**Blood Pressure and Interpregnancy Interval**

Both systolic and diastolic blood pressure followed a very similar pattern to MAP over the course of the two pregnancies. When each pregnancy was viewed as a whole, rather than as individual trimesters, both systolic and diastolic blood pressures were significantly reduced with interpregnancy intervals of <24 months and 24-48 months. When trimesters were compared, the systolic and diastolic blood pressures were significantly reduced only in the third trimesters of both subject groups. Since both systolic and diastolic blood pressures follow a similar pattern to mean arterial pressure across the pregnancies, this suggests that both values are contributing to the change in MAP across the two pregnancies. It has been observed that women diagnosed with preeclampsia had both elevated systolic and diastolic pressure when compared to women who experienced normal pregnancies (Hladunewich et al., 2011). Our data suggests that in the second pregnancies, both systolic and diastolic blood pressures are influencing the observed decrease in MAP.
Pulse Pressure and Interpregnancy Interval

Pulse pressure can be used as a measure of blood vessel elasticity, or arterial compliance. An increase in pulse pressure reflects a decrease in arterial compliance, and it has been observed that a higher pulse pressure is associated with an increased risk of preeclampsia (Dart & Kingwell, 2001; Hale et al., 2010). With this knowledge, it is no surprise that consistent with systolic and diastolic blood pressures, pulse pressure follow a similar pattern to MAP in the second pregnancies. The decrease in pulse pressure in the second pregnancies supports the finding that in preeclamptic pregnancies, there is increased pulse pressure suggestive of decreased arterial compliance.

Our data showed that the changes in third trimester pulse pressure across pregnancies were only significant with interpregnancy intervals of <24 months and 24-48 months. This suggests that at the longer interpregnancy interval, the increase in arterial compliance, which can serve as a protective function, begins to diminish, or that our ability to identify real differences was diminished by the reduced number of pregnancies with prolonged interpregnancy interval. As the arterial compliance decreases with longer interpregnancy interval, we believe that this allows for an increased risk of preeclampsia recurrence. In the current study, there was a trend towards more cases of preeclampsia in the second pregnancies as the interpregnancy interval grew longer, which is what would be expected after analyzing the pulse pressure results.

It is noteworthy that when the changes in pulse pressure between the two pregnancies on the first day postpartum were compared, there appeared to be an
association between change in pulse pressure and length of interpregnancy interval as well. When the interpregnancy interval was between 28-48 months, the pulse pressure on the first day postpartum of the second pregnancies was significantly lower than that of the first pregnancies. The opposite trend was seen when the interpregnancy interval exceeded 48 months. This further supports the argument that the decrease in arterial compliance begins to diminish at greater interpregnancy intervals and that this may manifest in the early postpartum window as well.

Preeclampsia Recurrence and Interpregnancy Interval

Preeclampsia is often referred to as “a disease of the first pregnancy” (Castiglioni et al., 2014). Although there have been a multitude of theories, it is largely unknown as to why the disease does not occur at the same rate in nulliparous and multiparous women. We hypothesized that the low recurrence rate of preeclampsia was due to the cardiovascular modifications that occur during first pregnancies, protecting the maternal system from dangerously high blood pressures in subsequent pregnancies. In this study, the recurrence rate of preeclampsia was 23%, which was in agreement with recurrence rate found in existing literature (McDonald et al., 2009; van Rijn et al., 2006). When hypertension did recur in second pregnancies, it was often less severe. For instance, a number of the subjects were diagnosed with gestational hypertension during their second pregnancy. Gestational hypertension is defined by high blood pressure occurring during pregnancy, without the other features of preeclampsia,
such as proteinuria ("Preeclampsia and High Blood Pressure During Pregnancy - ACOG," n.d.). When recurrence was compared among subjects who exhibited severe features of preeclampsia in the first pregnancy with those who did not exhibit such symptoms, the percentage of normal, uncomplicated second pregnancies was approximately equal. This suggests that the overall risk of recurrence of preeclampsia remains approximately the same, regardless of the severity of the preeclampsia during the first pregnancy in this cohort and in contrast to other studies (McDonald et al., 2009; van Rijn et al., 2006). However, a greater percentage of subjects developed severe preeclampsia in the second pregnancy when they were diagnosed with severe preeclampsia during the first pregnancy, compared to subjects who did not develop the severe features of the disease during their first pregnancy. This suggests that although the risk of developing preeclampsia is approximately equal regardless of severity of disease during the first pregnancy, those subjects who did experience a recurrence were more likely to exhibit severe features in the second pregnancy if they had exhibited these symptoms in their first pregnancy.

Although we found no significant difference in the rate of recurrence as the interpregnancy interval increased from <24 months to >48 months, there was a consistent increasing trend of recurrence in preeclampsia with a longer interpregnancy interval. The recurrence of severe preeclampsia, specifically, followed the same pattern in relation to interpregnancy interval. Epidemiological data suggests that the risk of preeclampsia returns near the nulliparous baseline at interpregnancy intervals of ten years or greater (Skjaerven et al., 2002).
Further research must be conducted on the recurrence rate of subjects with interpregnancy intervals within this range. We hypothesize that the inclusion of longer interpregnancy intervals would result in clearer associations to blood pressure changes and preeclampsia recurrence.

Conclusions

In conclusion, our data suggests that the interval between pregnancies does have an influence on the changes in mean arterial pressure, systolic blood pressure, diastolic blood pressure, and pulse pressure in subsequent pregnancies in women who were previously diagnosed with preeclampsia in their first pregnancies. With longer interpregnancy intervals, there was a smaller degree of change in these cardiovascular variables between the first, preeclamptic pregnancies, and the subsequent pregnancies. Although the association between interpregnancy interval was not significantly associated with the recurrence of preeclampsia, we hypothesize that there would be a more conclusive result if additional data was collected on subjects with interpregnancy intervals approaching ten years or greater. Hopefully, with the knowledge gained from this study, we will be able to focus our research goals and continue to gain insight into the pathophysiologic mechanisms of preeclampsia.
APPENDIX

Demographic Info:

Study I.D: _______ MRN: _____________ Year of Birth _________
Race: _____ Height: ___ (in) Prepregnancy Weight: ____ Highest Level Ed: _____
Tobacco: Y / N

Pregnancy Info:

Gravity: 1 2 3 4 5 6 7 8 Parity: 1 2 3 4 5 6 7 8 #SAB's: 1 2 3 4 5 6 7 8
Previous Delivery @ FAHC? Y/ N Date of last delivery: __/__/__
Total # ANV: ___
Number of Living Children: ______
Pregnancy Dating (U/S before 20 weeks)? Y / N Total Weight Gained (lbs): ___

PMHx of any of the following (if yes; explain:)

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Antenatal Blood Pressure Recordings:

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<th>EGA (weeks)</th>
<th>BP (systolic)</th>
<th>BP (diastolic)</th>
<th>EGA (weeks)</th>
<th>BP (systolic)</th>
<th>BP (diastolic)</th>
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</table>
Intrapartum/ Postpartum:

GH: Y / N  Date/time of delivery: _/_/_ @ ___

PEC: Y / N  EGA @ delivery: ___ ___ + ___

PEC (severe): Y / N  Birth Weight (grams): _______

HELLP: Y / N  Apgar 1/5: ___ / ___

Postpartum BP @ approx. 24 hours (with time): _____ @ ______

Med use in pregnancy? Y/ N

If yes, list: 1.

2.

3.

4.
LIST OF JOURNAL ABBREVIATIONS

BMJ  BMJ: British Medical Journal
REFERENCES


Osol, G., & Bernstein, I. (n.d.). Preeclampsia and Maternal Cardiovascular Disease: Consequence or Predisposition?

Preeclampsia and High Blood Pressure During Pregnancy - ACOG. (n.d.). Retrieved February 25, 2015, from
http://www.acog.org/Patients/FAQs/Preeclampsia-and-High-Blood-Pressure-During-Pregnancy


CURRICULUM VITAE

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EDUCATION

Boston College, College of Arts and Sciences; Chestnut Hill, MA
Bachelor of Science in Biology
GPA 3.597/4.00, Dean’s List
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Masters of Science in Medical Sciences
Anticipated May 2015

The University of Sydney; Sydney, Australia
Study Abroad Program, Spring 2012

WORK EXPERIENCE

Law Office Of Gregory P. Howe; Newport, VT
Legal Assistant
2005-2009
• Conducted research on non legal issues for trial preparation
• Delivered paperwork to courts, process servers, and law offices
• Handled scheduling and greeted clients

Newport Veterinary Hospital; Newport, Vermont
Summer Clinical Observation
Summer 2010
• Observed laboratory analysis, surgical interventions, x-rays and research techniques in the diagnosis, treatment and follow-up care of the animals
• Greeted the patients and answered any questions regarding pre-operation and post-operation care

VOLUNTEER EXPERIENCE

Boston College; Chestnut Hill, MA
Tutor
2009-2013
• Served as a Chemistry and Biology tutor for college students during school breaks
• Helped high school students prepare for the SAT and the ACT exams

Brigham and Women’s Faulkner Hospital; Boston, MA
Volunteer
2012-2013
• Organized and filed charts, sent appointment reminders to clients, and greeted patients in the Pain Clinic

• Registered patients for mammograms and helped them to understand the process and techniques

• Guided patients and families to various hospital departments

RESEARCH EXPERIENCE
Investigation in Molecular Cell Biology, Boston College Fall 2010
• Used plasmid complementation to study the functional conservation of various genes involved in methionine synthesis and metabolism of S. cerevisiae

• Used online databases and primary scientific research to analyze experimental results

Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Vermont 2014-2015
• Investigating how prior Preeclampsia and time interval between pregnancies affects blood pressures in subsequent pregnancies

• Researching the affects of obesity and body fat distribution on hemodynamic variables linked to an increased risk of preeclampsia

AWARDS
• CVRI Travel Award 2015