Revisiting the Link between Preeclampsia, Eclampsia and Seasonal Variation: An Analysis of over 39,000 Deliveries in West Michigan from 2005 to 2010

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Introduction

Preeclampsia and eclampsia (PreE/E) is a syndrome affecting multiple organ systems with symptoms including severe headache, vision changes, right upper-quadrant pain, nausea and vomiting, dizziness, and edema. In the United States, 2–7% of first-time pregnancies are complicated by PreE/E, which are characterized by new-onset hypertension with concurrent proteinuria after 20 weeks gestation. In Canada, women who emigrated from Hispanic, Sub-Saharan African, or Caribbean countries were three times more likely than women from industrialized nations to develop PreE/E. This disorder causes significant fetal and maternal morbidity and its basic pathophysiology is not well-understood. As a result, PreE/E presents significant challenges to clinicians who seek to provide the best outcomes for both their patients and their infants.

Studies have emerged that analyze the role vitamin D deficiency plays in the development and progression of PreE/E. Low serum vitamin D levels in pregnant women have been found to increase the risk of PreE/E and vitamin D deficiency may be an independent risk factor for developing PreE/E. Similarly, studies have shown that serum Vitamin D levels fluctuate with exposure to sunshine. In a group of women of childbearing age, sunlight exposure during May-October was significantly and independently associated with lower prevalence ratios of vitamin D deficiency and inadequacy. Vitamin D levels of healthy Canadians were highest in the summer and lowest in the fall and spring. Vitamin D levels of people living in West Michigan tend to follow the same trend during the winter. A random sample of patients who had their blood drawn over 12 weeks from January to April had an average vitamin D level of 17.43 ng/ml, Males had a level on average of 16.3 ng/ml and women had an average of 17.6 ng/ml. Both of these averages are well below the accepted total vitamin D reference values of 25-80 ng/ml. Since sun exposure is west Michigan is similar to the southern tier of provinces in Canada, we performed a population-based survey of PreE/E and correlated it with sun exposure. Our goal was to add insight into the debate of the importance of vitamin D in pregnancy, and thereby to help indicate if vitamin D levels should routinely be drawn during pregnancy.

Weather Patterns in West Michigan

Out of 174 U.S. cities and towns listed by the National Climatic Data Center, Grand Rapids in West Michigan is number 161 in percent of annual available sunshine received (46%). The area’s weather is determined by its latitude and eastern proximity to Lake Michigan; this location receives lake effect snow, rain, and heavy cloud coverage. Because there is less sunshine received in this region, we wanted to evaluate whether there is a strong correlation between available sunlight and pregnancy complications.

This report describes the outcomes of over 39,000 births in West Michigan in relation to the total available minutes of sunshine in the preceding trimester prior to the births. A strong correlation between PreE/E rates and total amount of sunshine was observed. We briefly describe the methods and results of the findings in this report.

Pathophysiology

Vitamin D deficiency has been implicated in many disorders including hypertension, end-stage renal disease (ESRD), diabetes, heart disease, inflammatory disorders, and increased cancer risk. Because the vitamin D receptor (VDR) modulates transcription of hundreds of genes and is expressed in many cells in the human body, it affects multiple organ systems. A low serum vitamin D level is associated with many disease processes, including those affecting the cardiovascular and renal systems.

Vitamin D deficiency is a well-established marker for cardiovascular disease and hypertension. Studies examining the link between vitamin D and cardiovascular disease show an increase in cardiovascular mortality during seasons in which Ultra Violet B radiation exposure is low. Hypovitaminosis D is associated with el-
evated mortality from cardiovascular illness.\textsuperscript{30,24,26,27} Furthermore, multiple studies have linked vitamin D deficiency to hypertension by vitamin D’s effect on renin.\textsuperscript{32,34-41} In 2007, Yuan et al. showed vitamin D supprresses expression of a renin promoter gene indicating that low Vitamin D levels could activate the renin angiotensin system.\textsuperscript{34} Vitamin D’s renal effects extend beyond the renin-angiotensin system. Extensive study of patients with ESRD has established low Vitamin D is associated with the development of albuminuria and inflammation.

### Vitamin D Deficiency and the Development of Preeclampsia/Eclampsia

The combination of renal protein wasting and systemic inflammation is a hallmark of PreE/E and led to the hypothesis that vitamin D deficiency may be involved in the pathogenesis of PreE/E.\textsuperscript{39} Research shows that a correlation exists between hypovitaminosis D and PreE/E as well as other complications of pregnancy.\textsuperscript{56-57} This relationship is supported by studies that show that decidual and trophoblastic cells both make and respond to vitamin D and that vitamin D aids in implantation.\textsuperscript{56-67} Furthermore, a Norwegian survey study indicated that women who take vitamin D supplements have substantial reduction in PreE/E; however, because vitamin D intake in this population is correlated with omega-3 intake it was not possible to rule out a benefit from long chain fatty acids in the diet.\textsuperscript{58}

### Materials and Methods

Using de-identified data, and adhering to IRB protocols, the electronic medical record database of Spectrum Health, a multi-hospital network in West Michigan predominantly serving Kent County, was searched from June of 2005 through May of 2010 to construct the PreE/E rate. The five most current years were used because after mid 2005, deliveries reached steady state as labor and delivery was concentrated at one of the Spectrum Health hospitals. A rate was calculated for each calendar month over those five years from all live births using the Spectrum Health hospitals. A rate was calculated for each month in the five-year period being examined as well as the three months prior to the diagnosis of Pre/E was recorded and analyzed. This allowed for the comparison of PreE/E rates in any month to the potential influence of vitamin D from accumulated sunlight exposure in prior months. In order to work with positive integers, minutes of darkness were derived from the sunlight data by subtracting the minutes of sunlight from the total minutes in each month. The minutes of darkness for the month were then divided by the number of days in each month to obtain the average minutes of darkness per day in each month. A similar calculation was performed to find the average minutes of darkness per day in the three months prior to the month of the PreE/E rate.

Vitamin D precursor molecules have half-lives of many weeks, which can lead to significant accumulation over an extended period of sun exposure.\textsuperscript{69} The correlation between available sunlight and PreE/E rate was examined using the average minutes of darkness per day for the one-month period and the three-month period prior to the month of the PreE/E rate. In order to have a more powerful dataset the PreE/E rate of each month of each year was used individually, giving 60 data points. The Pearson product moment correlation coefficient was calculated as a measure of the linear relationship between the of PreE/E rate for each month and the aforementioned corresponding 1 month and 3 month prior period’s average minutes of darkness. PreE/E rate was calculated as the total of PreE/E cases in each month divided by the total live births in that month. A p value <0.05 was considered to be significant. Correlations were calculated using SPSS, version 19, and checked for accuracy in Microsoft Excel. The 95% confidence intervals for rates were calculated in Excel using the Normal Approximation Method. Graphical representations of the data were created in Microsoft Excel 2003 (Bar Charts) and SPSS, version 19 ( Scatter plot). A confidence interval graph was created with Open Office, version 1.1.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>642.4</td>
<td>Mild or Unspecified Pre-eclampsia</td>
</tr>
<tr>
<td>642.5</td>
<td>Severe Pre-eclampsia</td>
</tr>
<tr>
<td>642.6</td>
<td>Eclampsia</td>
</tr>
<tr>
<td>642.7</td>
<td>Pre-eclampsia or eclampsia superimposed on pre-existing hypertension</td>
</tr>
</tbody>
</table>

\textsuperscript{4}International Classification of Diseases

The PreE/E rate from this data was then compared to minutes of available sunlight in West Michigan using public domain information from the National Weather Service. Specifically, the total number of minutes of actual sunshine received at the Grand Rapids, Michigan weather station for each month in the five-year period being examined as well as the three months prior to the diagnosis of Pre/E was recorded and analyzed. This allowed for the comparison of PreE/E rates in any month to the potential influence of vitamin D from accumulated sunlight exposure in prior months. In order to work with positive integers, minutes of darkness were derived from the sunlight data by subtracting the minutes of sunlight from the total minutes in each month. The minutes of darkness for the month were then divided by the number of days in each month to obtain the average minutes of darkness per day in each month. A similar calculation was performed to find the average minutes of darkness per day in the three months prior to the month of the PreE/E rate.

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**Figure 1.** The 95% Confidence intervals for the Preeclampsia/Eclampsia rate over the five-year period of the study. Comparison of the peak rate in December to the trough rate in September and that in the low sun months of December through April to the high sun months of July through September.
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Results

There were 39,337 total live births during the five-year period under observation and 2,607 cases recorded as preeclampsia or eclampsia (Table 2) with delivery for a global rate of 6.63% (95% CIs [0.0638, 0.0688]). The rate varied from a high of 7.76% (95% CIs [0.0681, 0.071]) in December to a low of 5.30% in September (95% CIs [0.0455, 0.0605]), a 32% reduction from peak to trough. Inversely this represents a 46% increase from September to December. The difference between the peak and trough rates is statistically significant at the 95% level. The average rate from the five low sun months of December through April was 7.32% (95% CIs [0.0691, 0.0772]) and for the high sun months of July through September was 5.64% (95% CIs [0.0525, 0.0603]); these numbers yield a relative increase of 30%, which is also statistically significant at the 95% level. These confidence intervals can be seen in Figure 1.

Table 2. Summary Stats – PIH vs. Live Births

<table>
<thead>
<tr>
<th>Total Live Births</th>
<th>PIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Patients</td>
<td>39,337</td>
</tr>
</tbody>
</table>

Age Averages:

- Mean: 27
- Median: 27
- Mode: 26

Age Range: 14 thru 49

Age Bracket % of Total:

- 14-19: 11.25% vs 9.94%
- 20-24: 26.39% vs 24.21%
- 25-29: 30.33% vs 30.81%
- 30-34: 21.49% vs 21.83%
- 35-39: 8.72% vs 10.02%
- 40-49: 1.82% vs 3.18%
- 50+: 100.00% vs 100.00%

Race % of Total

- White: 67.48% vs 65.71%
- Black: 13.02% vs 13.96%
- Hispanic: 10.06% vs 10.28%
- Unknown: 6.44% vs 8.55%
- All Others: 3.54% vs 2.15%

(Note that Race/Ethnicity percentages add to slightly more than 100, due to Hispanic/Black and Hispanic/White counting in more than one group)

The general pattern of the PreE/E rate from 2005 through 2010 and the average minutes of darkness in the preceding three-month period can be seen in Figure 2.

There was a significant positive correlation ($r = 0.364, p = 0.004$) between the PreE/E rate and the prior three months’ average minutes of darkness per day. This correlation can be seen in Figure 3.

There was also a significant positive correlation ($r = 0.358, p = 0.005$) between the PreE/E rate and the prior month’s average minutes of darkness per day.

Discussion

Our findings suggest a strong relationship between available sunlight in the three months and 1 month prior to delivery and the rate of PreE/E and further distinguish the differences in the PreE/E rate when comparing summer to winter. There have also been reports of regional variation around the world with reductions in pre-eclampsia the closer the region is to the equator. Grand Rapids, Michigan where the data was collected is on the 43rd latitude north and had an overall prevalence of 6.63%. In Beijing, China, at the 39th latitude north, the prevalence of pre-eclampsia is 5.7%. In Hong Kong, at the 22nd latitude north, the risk of pre-eclampsia has been reported to be 1.6%. We found a 32% increase in the PreE/E rate for births in December compared to births in September. The difference between the peak and trough rates is statistically significant at the 95% level. These confidence intervals can be seen in Figure 1.

Figure 2. Comparison of seasonal pattern of Preeclampsia/Eclampsia rate with that of average minutes of darkness (no sunlight) per day in prior three-month period

Figure 3. Scatter plot with best-fit line showing where each of the 60 months in the five-year period analyzed fall in terms of Preeclampsia/Eclampsia rate and average minutes of darkness (no sunlight) in the prior three-month period
in September. Although vitamin D levels were not obtained in this study, these findings may support current theories that hypovitaminosis D plays a role in the pathogenesis of PreE/E and hypovitaminosis D peaks in the fall and winter months, providing a different perspective on the vitamin D connection. Because sunshine is associated with vitamin D production, vitamin D serum levels are highest in months where sunshine is most prevalent, and vitamin D has been implicated in the development of hypertension and PreE/E, it is likely that increased sunshine reduces the risk of PreE/E.

Similar to findings of seasonal variation in hypertension rates in pregnant women, our findings lend credence to the importance of obtaining sufficient sun exposure in the second and third trimesters to help reduce a woman’s risk of PreE/E. A meta-analysis of the literature examining the relationship between seasonal variation and hypertension, pre-eclampsia, and eclampsia rates reported 11 out of 14 studies showed an increase in pre-eclampsia in the winter months in non-tropical climates. Furthermore, a large Australian study has shown that the amount of sunlight during the time closest to birth is a better predictor of the onset of hypertension in pregnancy than the amount of sunlight at conception.

Potential Confounders

Future studies to evaluate the correlation between seasonal variation and PreE/E should report vitamin D levels, and address potential confounders such as race, obesity, and levels of exercise, depression and migraine, or maternal infection all of which may contribute to hypovitaminosis D. Research so far has found considerable support for the role of diet in preventing PreE/E. Studies show that the high intake of vegetables, fiber, milk, and foods rich in potassium reduce the risk of PreE/E while a diet high in processed meat, calorie-rich foods, sweet drinks, and salty snacks increase the risk of PreE/E. Other morbidities such as depression and migraine, which could have an effect on behavior, have also been examined and are associated with an increased risk of PreE/E. Consequently, while the results of this study suggest an inverse association between sunlight exposure and PreE/E, this may be just one factor of many contributing to this disease.

Recommendations

These findings suggest that pregnant women in clouder climates may be more likely to develop Pre/E in the fall and winter seasons. Due to the potentially life-threatening effects of PreE/E, it may be necessary to test serum Vitamin D levels in all women at the end of the first trimester or at 20 weeks gestation. Alternatively, women who have an increased risk of developing PreE/E due to obesity, race, or clouder climates should have their Vitamin D levels checked at the end of the first trimester and all pregnant women should take Vitamin D supplements daily along with their prenatal vitamins to help prevent hypovitaminosis D leading up to PreE/E. While the cost-effectiveness of drawing vitamin D levels on pregnant women is yet to be determined, lifestyle changes that promote outdoor physical activity and sun exposure may reduce the morbidity associated with PreE/E. We should educate our patients to “live summer year round” by encouraging pregnant women to exercise during the winter, eat more fruits and vegetables, and in a region with as little sunshine as West Michigan, take a vitamin D supplement with consumption guided by repeated serum blood levels.

The Institute of Medicine stated that while substantial evidence exists linking levels of vitamin D with bone health, current evidence does not support other benefits of vitamin D supplementation. While this statement may hold true for many Americans, we believe that sufficient evidence exists for the monitoring and treatment of hypovitaminosis D in specific populations. Examples of such populations include African Americans, Hispanics, those with chronic kidney disease and pregnant women living in areas of little sun exposure especially in the winter. Further research into the role of vitamin D deficiency in the risk of PreE/E is needed.

Conclusion

PreE/E was 32% more common during the winter in West Michigan when compared to the average during the summer. There was a moderately strong correlation with the number of minutes of darkness in the three months preceding the ensuing month’s Pre/E rate. This suggests a possible link to vitamin D status, but other lifestyle influences cannot be ruled out. Future studies should be carried out to assess potential confounders like race, and pregnant women should be encouraged to take vitamin D supplements daily, particularly in the fall and winter seasons.

Acknowledgements


Abbreviations

ESDR = end-stage renal disease
PreE/E = preeclampsia/eclampsia
VD = vitamin D receptor

References


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