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A pilot study of the relationship between preeclampsia and anti-tetanus toxoid antibody levels

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1. Introduction

Pregnancy is a fascinating immunological event in which the mother does not reject the fetus although it represents a foreign body for nearly nine months. The placenta serves a vital role in protecting the fetus from potential maternal immunological reactivity by several mechanisms including a shift from type 1 to type 2 cytokine production by T cells and NK cells, fetal histocompatibility antigen expression such as HLA-G, and the restriction of antibodies that may cross the placental barrier [1–11]. Only maternal IgG crosses the placenta and furthermore only the subclasses 1, 3, and 4 [12–15]. Recent work has identified that there is a unique maternal IgG1k that is found in placenta tissue (p-IgG1k) and could be contributing to balancing the immunological activity at the maternal-fetal interface [16]. When the heavy chain of this p-IgG1k (identified as accession number AAH90938.1 on BLAST protein data search) is cross matched to other proteins, interestingly anti-tetanus toxoid antibody appears among the possible protein matches. Therefore the question arose whether the gestational level of the anti-tetanus toxoid antibody correlates in any way with pregnancy outcomes – especially preeclampsia.

Preeclampsia is a significant medical condition occurring in 5–8% of pregnancies and contributes to both maternal and fetal complications [17]. Preeclampsia accounts for about 15% of premature births in the United States, and worldwide about 76,000 pregnant women die each year from preeclampsia and associated hypertensive disorders. Preeclampsia is characterized by hypertension and proteinuria that develop after gestational week 20, but the syndrome can also be associated with other clinical features such as significant nausea, vomiting, headaches, visual disturbances, pulmonary edema, thrombocytopenia, hemolytic anemia, and/or elevated liver transaminases [17–19]. The syndrome has been classified into “early-onset” preeclampsia (< 34 weeks), and “late-onset” preeclampsia (≥ 34 weeks) to better identify risk factors, prognosis, and outcomes [20]. “Early-onset” preeclampsia has a higher risk of maternal and fetal complications compared to “late-onset” preeclampsia [20,21]. Therefore the gestational age of onset of preeclampsia plays a significant role in maternal and fetal outcomes, and finding a laboratory test could distinguish between “early-onset” and “late-onset” disease would be very helpful. Attempts are ongoing to find such a test(s) but to date no single marker has been proven to predict and/or distinguish between these two forms of preeclampsia [22,23].

Preeclampsia in the early stages of development appears to involve incomplete transformation of the maternal spiral arteries – thereby over time causing a mismatch with fetal nutritional demands exceeding placental supply [20,21]. This state of hypo perfusion sets into motion production of inflammatory products, and angiogenic and anti-angiogenic factors due to tissue hypoxia – which manifests subsequently as preeclampsia/eclampsia [24,25]. The hypothesis presented in this article is that a unique idiotypic maternal IgG1k crosses into the placenta and may modulate the inflammatory process which is important in spiral artery remodeling [16]. Since this p-IgG1k may be closely associated with anti-tetanus toxoid antibodies, the hypothesis proposed by this study is that women with low anti-tetanus toxoid levels may be more prone to developing preeclampsia or toxemia compared to women who do not develop preeclampsia or toxemia. Furthermore the work shown in this paper suggests that the gestational anti-tetanus toxoid antibody level may have a significant role in distinguishing between “early-onset” and “late-onset” preeclampsia.

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2. Methods and patients

A total of 959 pregnant women attending the maternity clinic of author GL were invited over a two year period to participate in this clinical research study for which 145 agreed with appropriate informed consent to participate (15.1%). Because this sample is not randomized in any sense, the conclusions of the analysis are limited – but nearly every pregnant woman during the time period of this study was invited to participate in the study. For each consenting patient a sample of blood was drawn at gestational week 28 and tested for quantitative anti-tetanus toxoid antibody levels (LabCorp, Pocatello, Idaho). Each patient also provided additional information regarding their general health and maternity history inclusive of age, BMI at week 28, number of pregnancies including this pregnancy, number of miscarriages, history of non-pregnancy hypertension, history of diabetes, personal and/or family history of preeclampsia, and smoking history. Subsequently, each patient's medical history was then followed inclusive of pregnancy outcome, history of gestational hypertension, and history of preeclampsia or toxemia, and fetal health at time of delivery.

The definition of preeclampsia used in this study required that a patient have systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 on two separate occasions, AND proteinuria ≥ 300 mg/24 h, OR in the absence of these features the patient had new onset thrombocytopenia ($< 100{,}000$/ul), elevated liver transaminases ≥ 2x ULN, renal insufficiency with serum creatinine > 1.1 mg/dL, pulmonary edema, or cerebral symptoms (moderate to severe headaches), and/or significant changes or loss of vision, or HELLP syndrome [17–19].

To examine for any bias in this study, a retrospective analysis of the non study group was performed identifying those subjects who developed gestational hypertension (without preeclampsia) and then compared those subjects to the study patients with gestational hypertension (without preeclampsia). This analysis revealed that 26 subjects met criteria for gestational hypertension in the non study group (26/814) compared to the study group (5/145) and used the guidelines for defining gestational hypertension found in the Task Force on Hypertension in Pregnancy [18].

The hypothesis for this pilot study is that patients with lower levels of anti-tetanus toxoid antibody at gestational week 28 are at increased risk of developing preeclampsia. With only 145 patients we would expect less than 12 patients to develop preeclampsia – based on a possible incidence of 5–8%. With such a small number of patients, the statistical analysis is limited. However, we can test this primary hypothesis using the Wilcoxon rank sum test which compares the median values of the patients developing preeclampsia with those who do not.

3. Results

A sample of 145 pregnant women were recruited into this observational study with appropriate informed consent and their anti-tetanus toxoid antibody levels were determined at gestational week 28 and then followed during the course of their pregnancy. The distribution of anti-tetanus toxoid antibody values for these 145 patients is shown in Fig. 1 with a sample median of 1.31 IU/ml. Also other features inclusive of age, total number of pregnancies, prior history of preeclampsia, and prior history of gestational hypertension were examined in comparing normal pregnant women and those with preeclampsia with regards to their respective anti-tetanus toxoid antibody levels (Table 1). Of the nine women who developed preeclampsia in this pilot study, interestingly 4/9 cases had anti-tetanus toxoid antibody levels between 0 and 0.5 IU/ml (at one extreme), 2/9 cases had levels between 2.51 and 3 IU/ml (at another extreme) – suggesting a bimodal distribution of anti-tetanus toxoid antibody levels with regards to preeclampsia. Of the nine subjects out of 145 subjects (6.2%) who were diagnosed with preeclampsia, seven of these nine patients met the criteria for preeclampsia by manifesting gestational hypertension and proteinuria (patient numbers 33, 40, 46, 79, 101, 102, and 125), and two patients met the modified criteria by having clinical features of significant headaches, blurred vision, intense nausea and abdominal pains (patient number 20), and hypertension with significant headaches, blurred vision (patient number 44). The data from Fig. 1 and Table 1 show this bimodal distribution which is very reminiscent of the concept of "early-onset" and "late-onset" preeclampsia. Based on the bimodal distribution observed here in this study, "early-onset" (or preterm) preeclampsia could be redefined as preeclampsia from week 20 to before week 36, and "late-onset" (or term) preeclampsia could be redefined as on and after week 36. Based on this redefinition, then there were 7/9 subjects with "early-onset" preeclampsia with a mean anti-tetanus toxoid antibody level 0.67 IU/ml, and 2/9 subjects with "late-onset" preeclampsia with a mean level 2.79 IU/ml (Fig. 2).

We performed the Wilcoxon signed rank test to compare median anti-tetanus toxoid antibody levels for patients developing preeclampsia with those who do not. This was done for both the early-onset preeclampsia patients and the gestational hypertension patients. The p-value of 0.011 for the test of the early-onset preeclampsia patients indicates that these patients have statistically lower median anti-tetanus toxoid antibody levels (0.32 IU/ml) than the median of those patients not developing preeclampsia (1.32 IU/ml). Since this probability is less than 0.05, we conclude that the preeclampsia patients do not have the same distribution of anti-tetanus toxoid antibodies. Use of the anti-tetanus antibody levels provides a biomarker for increased risk of early-onset preeclampsia in differentiating between preterm and term preeclampsia.

There were five subjects in the study group who did not meet criteria for preeclampsia but met criteria for gestational hypertension. The distribution of the anti-tetanus toxoid antibody levels for these patients did not show any particular pattern (Fig. 3), and the sample median was 1.24 IU/ml which was not statistically different from the total sample median of 1.31 IU/with a p-value > 0.10, indicating that the anti-tetanus antibody levels have no relationship to the development of gestational hypertension.

To examine for any possible bias in comparing the study and non study groups, the number of women with gestational hypertension in the non-study group (26 or 3.4%) were compared with the study group (5 or 3.2%). There is no evidence that the proportion of pregnancies developing gestational hypertension was different between the two groups (p-value > 0.10). Also the incidence of preeclampsia is reported to be 5–8% for the general population for which this report showed an incidence of 6.2% – again suggesting that the study group appears to be similar to the general population.

4. Discussion

Preeclampsia is a complex disease associated with maternal and fetal/placental factors that contribute to poor trophoblast invasion of maternal spiral arteries with inadequate remodeling, and subsequent hypo perfusion of placental tissue [17]. Placental tissue hypoxia then promotes increased expression of anti-angiogenic factors, and other stress related factors (such as syncytiotrophoblast microparticles, and proinflammatory cytokines) that contribute to the development of hypertension, proteinuria, and other clinical features of preeclampsia [17,21,24]. These features may have more to do with "early-onset" (or preterm) preeclampsia – and involve a combination of maternal and fetal factors that influence placental health. However "late-onset" (or term) preeclampsia may have more to do with maternal factors such as younger age, nulliparity, and diabetes that influence maternal health [26–28]. The hypothesis proposed in this study is that the maternal anti-tetanus toxoid antibody level may play a significant role in reducing the risk of preterm preeclampsia. Based on the finding of this small study, pregnant women at week 28 gestation with anti-tetanus toxoid antibody levels < 1.3 IU/ml (the sample median) may be at greater risk of preeclampsia. However this study is too limited to be definitive at