

Preeclampsia and Placenta Protein 13: Are they Exclusive?

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Received: September 13, 2019; Published: October 04, 2019

Abstract

One of the evaluated markers for early detection of preeclampsia is Placental Protein 13 (PP13), a member of the galectin superfamily. The PP13 level alone, or in combination with additional placental markers, individualized risk factor models, and biophysical biomarkers have been extensively studied in screening for preeclampsia and revealed promising detection rates that will be discussed throughout this review. Galectins including PP13 are expressed in normal tissues while often differentially expressed in cancer cells. As such, we searched TCGA and found that *LGALS13*, that encodes PP13, is mutated or amplified in various cancers.

Keywords: Pregnancy; Pre-Eclampsia; First Trimester Screening; Biomarkers; Placental Protein 13; Cancer

Preeclampsia in brief

Preeclampsia (PE) is an adverse outcome of pregnancy that affects 2 - 8% of all pregnancies with an increase in incidence of 25% in the past two decades [1,2]. Women with a history of PE are prone to development of future heart disease, stroke, and high blood pressure [3]. PE is a disorder of pregnancy associated with new onset hypertension that often occurs after the 20th week of gestation and frequently near term. Although hypertension is usually associated with a new onset of proteinuria (300 mg or more in 24hrs urine collection or creatinine/protein ratio of 0.3, or +2 urine dipstick), some women present with other symptoms and signs of PE in absence of proteinuria i.e. decreased platelets count $< 100.000 \times 10^9/L$, renal insufficiency (serum creatinine greater of 1.1 mg/dL or doubling of creatinine concentration in absence of other renal diseases), impaired liver functions (elevation of liver transaminases twice the normal concentration values), and pulmonary edema [4,5].

PE may have a graveyard prognosis: if left untreated, it evolves to eclampsia, which is one of the top five causes of maternal mortality. Eclampsia is responsible for a maternal death every 12 minutes [6]. According to the pregnancy mortality surveillance system of the Centers for Disease Control, hypertensive disorders in pregnancy are one of the top 10 leading causes of pregnancy-related mortalities in the USA between 2011-2014 [7] (Figure 1). PE is responsible for 15% of premature births in industrialized countries and 25% of children born with iatrogenic very low birth weight ($< 1500g$) [8,9]. Uncontrolled chronic medical conditions, ethnicity (African American and Hispanic women), early and late ages of pregnancy, unhealthy lifestyle practices (such as lack of exercise) are all risk factors for PE development [10,11]. Therefore, simple lifestyle modifications and proper control of chronic diseases can reduce the burden of PE [12,13].

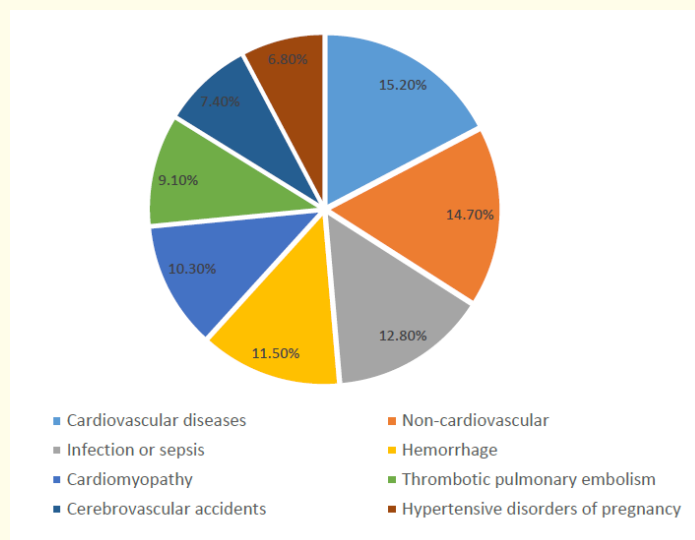


Figure 1: Top 10 leading causes of pregnancy-related mortalities.

In the absence of curative treatment for PE, prompt control of hypertension and eclampsia prophylaxis until delivery is the standard of care, whereas effective screening tools for early identification of pregnant women at high risk of PE are urgently needed [14]. Physicians rely mainly on patients' medical and obstetrical history to predict PE. Nowadays, besides risk factors from history, uterine artery Doppler velocimetry along with various biomarkers, such as placental growth factor (PGIF), soluble fms-like tyrosine kinase 1 (sFlt-1), soluble endoglin, and pregnancy associated placental protein-A (PAPP-A), are used to predict PE [15,16]. Early identification of pregnant women with PE will enable physicians to intervene effectively and deter any further maternal and neonatal complications [17]. One of the potential prophylactic measures is aspirin administration. Of note, the American College of Obstetrics and Gynecology (ACOG) recommends low dose aspirin administration before 16 weeks if women have a medical history of an early onset PE (before 34 weeks), preterm delivery, or PE in more than one pregnancy [18,19]. However, aspirin use at or after 16 weeks of pregnancy is ineffective in PE prevention, suggesting importance of early intervention [20].

Unfortunately, due to the multifactorial nature of PE pathogenesis and risk factors, no single reliable tool is yet available to predict PE earlier in its development [3,21]. Currently, based only on demographic data, proper medical and obstetrical history records, the detection rate (DR) ranges between 30 - 40% with a false positive rate (FPR) of 10%. Thus, alternative parametric approaches combining clinical risk factors with various biomarker levels have been extensively studied as mentioned above [22,23]. Currently, several methods of detection, including uterine artery pulsatility index (PI), mean arterial pressure (MAP), and maternal serum biomarkers including PAPP-A, PIGF, PP13, and fetal hemoglobin levels at 11 - 13 weeks' gestation, and maternal risk factors, are used to detect a high proportion of pregnant women with early PE, with better detection rates of PE with combinations of placental biomarkers [24,25].

In this review, we will discuss PP13 as a promising marker of PE alone as well as in combination with other markers. First, we will highlight the role of PP13 in both normal and PE associated pregnancy.

Placental protein 13 in pregnancy and preeclampsia

PP13, also called galectin 13, is one of the 56 currently identified placental proteins. It is a member of the galectin superfamily, a family of carbohydrate-binding proteins referred to as galactosidase-specific lectins [26]. Lectins bind beta-galactoside residues of proteins, and

as a result PP13 modulates various biological events, such as implantation, embryogenesis, cell death, and molecular recognition [27,28]. The PP13 protein is found primarily in placenta at the apical membrane of the syncytiotrophoblast [29].

In early placentation, PP13 binds beta and gamma-actin within trophoblasts, mediating trophoblast migration towards the placental bed and enhancing the release of prostacyclins for the vascular remodeling stage of the maternal spiral arteries within the uterus [30,31]. Studies on non-pregnant and pregnant rats demonstrated the reduction of systemic and local uterine vessel blood pressure upon PP13 infusion [32].

PP13 might work as a chemokine, forming zones of necrotic and apoptotic decidual cells, T cells, neutrophils, and macrophages through IL-1 alpha and IL-6 activation of resident decidual immune cells. PP13 aggregates may mediate maternal inflammatory responses outside the maternal spiral arterioles and in decidual veins during the first trimester. A failure of galectin 13-driven formation of necrotic and apoptotic areas during early placentation is suggested to be a part of the physiological events that occur in early PE [33].

LGAL13 is located on chromosome 19 and consists of a promoter region followed by four exons designated as E1-E4, separated by introns [30]. The study of the *LGALS13* sequence in PE patients from different ethnic groups revealed three types of mutations: (1) single nucleotide polymorphisms (SNP) with deletion of the T nucleotide in position 221 in exon 3 leading to a stop codon; (2) mutation at the intron-exon boundaries due to an intronic G to A conversion (Dex-2 mutation); and (3) 98A to C SNP in the promoter region that leads to truncated/misfolded proteins [34].

Placental protein 13 as a screening tool in preeclampsia

In healthy pregnancies, PP13 maternal serum levels increase throughout the pregnancy. In cases with PE, patients exhibit lower levels of PP13 in the first trimester; however, later after the onset of clinical symptoms and near delivery, PP13 levels reach above normal values [35]. In another study, asymptomatic pregnant women developed PE demonstrated lower levels of placental PP13 mRNA expression when compared to controls, suggesting that reduced PP13 mRNA expression between 10 - 14 gestational weeks is one of the possible earliest signs of PE [36,37]. Presumably, high PP13 serum levels in PE later in pregnancy, in spite of the low PP13 mRNA expression, are due to the increased syncytiotrophoblast microparticle (STBM) shedding from the placenta [38].

Given the deranged levels of PP13 in PE cases, several clinical studies assessed PP13 level in combination with other placental biomarkers to stratify pregnant women with a high risk of PE development. In a cohort of 300 Hispanic pregnant women at high risk of developing PE, of whom 50 patients developed a disease later on, the serum levels of PP13 between 8 - 13 weeks of pregnancy were lower in PE patients than in normal pregnancy [39]. The median first trimester maternal PP13 level after adjustment for gestational age, BMI, maternal age, and parity, was 1 in normal pregnancy and 0.59 in all cases of PE. First trimester PP13 levels revealed reliable results in screening for PE early in the first trimester, at 80% specificity, a cutoff of 0.39 multiple of median (MoM) had a sensitivity of 100% at early PE and 85% for preterm PE.

In a cohort of 1366 pregnant women, of which 20 women were diagnosed with PE later in pregnancy, the efficacy of PP13 was examined in different time points during pregnancy: first trimester between 6 - 10 week, second trimester between 16 - 20 week with routine testing, and 24 - 28 with glucose tolerance testing [40]. Findings revealed lower levels of PP13 in the 20 patients with PE when compared to the unaffected group of women. With a given specificity of 80%, PP13 testing showed a sensitivity of 80% in the first trimester, 33% between 16 - 20 gestational weeks, and 38% between 24 - 28 gestational weeks. Considering the higher PP13 levels later in pregnancy in PE patients, the significance of PP13 slope values in PE detection was assessed. At a specificity of 80%, with a slope cut off of 10 between 6 - 10 weeks to 16 - 20 weeks PP13 values, the sensitivity was 89%. An additional study evaluated the maternal serum level of PP13 at 9 - 13 weeks of gestation in a diverse population of 45 PE cases adjusted to 290 control subjects at Massachusetts General hospital [41]. In this study, the control group had a PP13 median of 123 pg/mL in the first trimester compared to 27.2 pg/mL for the PE group. First

trimester PP13 testing in 38 PE cases revealed a sensitivity of 79%, at 90% specificity, which is equal to an odds ratio of 32.1 (a 32 fold increased likelihood of PE in women with low vs normal PP13 levels). In another nested study, 88 PE cases were matched for gestational age with 446 controls, and first trimester serum levels of PP13 and PAPP-A were assessed to detect early PE cases [42]. All patients also underwent uterine artery Doppler velocimetry between 22-24 weeks to assess the mean pulsatility index (PI). At 80% specificity, serum PP13 testing could detect 50% of early PE cases, which is better than PAPP-A alone (23%), yet both were not as good as the 75% detection rate achieved by second trimester uterine artery Doppler alone. However, combining uterine artery Doppler with PP13 testing led to an increase in the detection rate to 79%.

An another study by Nicolaides, *et al.* examined uterine artery PI and PP13 levels at 11 weeks of gestation to end of first trimester in 10 early PE cases and 423 unaffected women [43]. With an FPR of 10%, PP13 and PI showed a detection rate of 80% and 40%, respectively, which was improved to 90% when combined. The last two studies differ in two major population characteristics that may explain the disparities in the detection rates. The first factor is ethnicity, as in the first study [42], 80% of the population comprised Caucasian women compared to 30% in a second study [43]. A second factor that could explain differences is the percentage of nulliparous pregnancies (49% vs 60% of all PE patients) in two studies performed in England.

Based on PP13 clinical study findings, we would like to make several suggestions for future consideration:

1. Using a specific Standard Operating Procedure protocol for blood drawing and storage for PP13 as these parameters can affect protein levels, which is especially important for proteins with low expression.
2. Combination of several markers for PE detection to improve specificity and sensitivity.
3. Further elucidation of PP13 function to discover if PP13 plays a role in all heterogeneous PE cases.
4. Investigation to determine if PP13 infusion can rescue PE diagnosis and how early it should be conducted to achieve desirable results.
5. Search for therapies that can increase the PP13 level early in pregnancy to reverse PE development.

Placenta protein 13 in cancer

Galectins has been found to participate in tumor development, invasiveness, and angiogenesis. They modulate both extracellular and intracellular functions that promote tumorigenesis through deregulated apoptosis and cell cycle [44]. Two of the most extensively studied galectins, galectin-1 and galectin-3, can interact with oncogenic proteins, such as Ras [45]. Because PP13 is a member of the galectins superfamily, we were intrigued to examine the link between PP13 and cancer.

Initially, certain levels of PP13 were found in some adult tissues and in liver adenocarcinoma and melanoma by using Western blot analysis and custom-made antibodies [46]. These findings were further debated and attributed to be non-specific based on Northern blot analysis. To assess whether *LGALS13* is relevant in cancer, we analyzed TCGA tumor data to assess PP13 expression in tumors. Apart from the previously described *LGALS13* mutations in PE, mutations of *LGALS13* have been observed in different types of cancer, including breast cancer, liver adenocarcinoma, lymphoma, and leukemia, which garnered attention to the role of *LGALS13* mutations in prognosis and management of these cancer patients [47]. Based on TCGA analysis of 261 different cancer studies, *LGALS13* mutations are located across all four exons and comprised from missense (106), truncating (22), and in-frame (3) (Figure 2A). Based on the analysis of more than 11,000 tumors from 33 of the most common malignancies (Pan-Cancer atlas project), 2% of the patient samples revealed *LGALS13* alterations [48]. Irrespective of the cancer type, patients with mutations are associated with reduced overall and disease free survival periods. Alterations (mutations + amplifications) most frequently occur in uterine, ovarian, lung, pancreatic, and cervical cancers respectively [48,49]. In high grade serous ovarian cancer (HGS), our cancer of interest, data from 584 patients revealed 53 cases had amplification of *LGALS13* [48,49] and these alterations were associated with reduced disease-free and total survival (Figure 2B and 2C). We found that HGS ovarian and uterine cancer exhibited increased amplification while other types of cancer showed genetic mutations

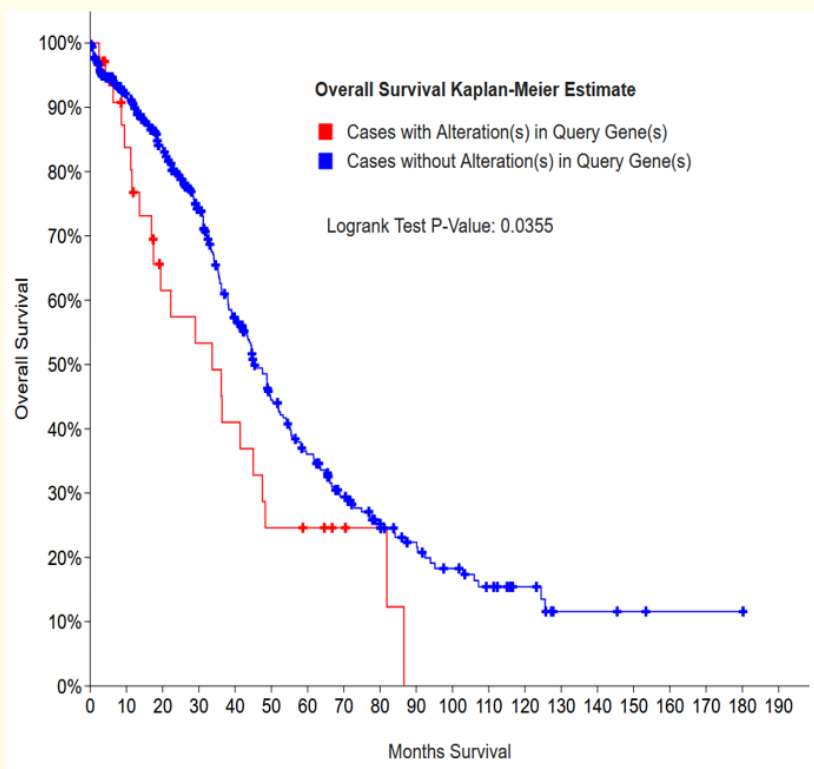
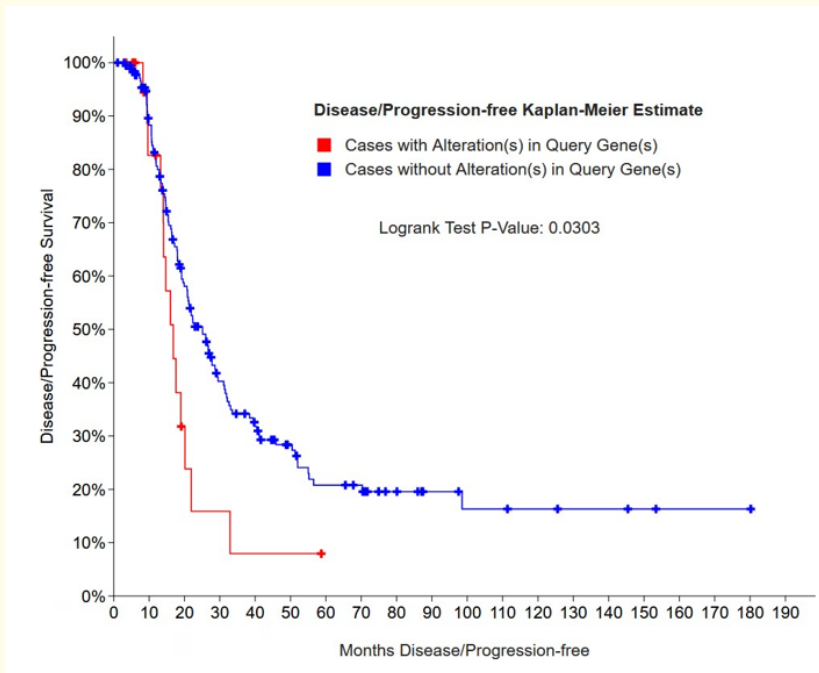
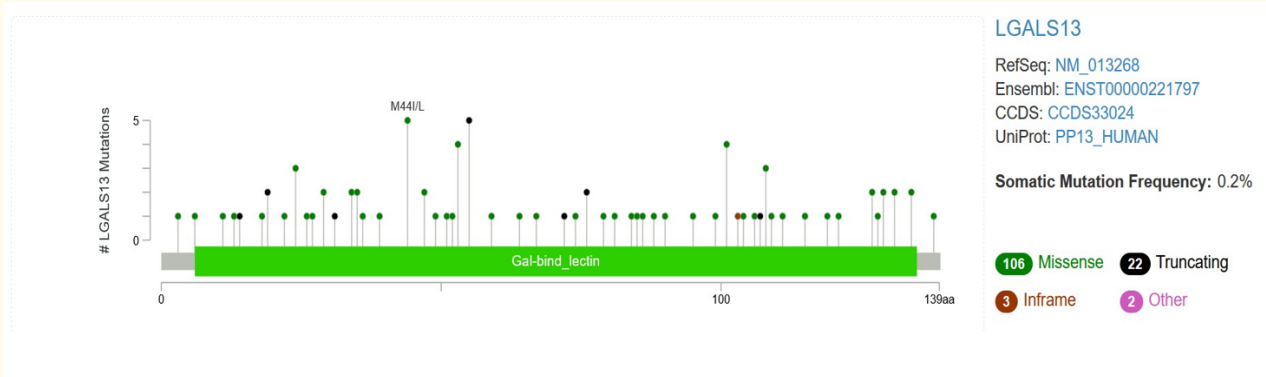


Figure 2: Placenta Protein 13 in cancer.

A: Mutations in LGALS13 based on TCGA analysis of 261 different cancer studies (133 Mutations: includes 47 duplicate mutations in patients with multiple samples).

B: Disease-free survival in 389 HGS tumors with mutation and CNA data.

C: Overall survival in 389 HGS tumors with mutation and CNA data.

	Total cases	No. of cases with alterations	Cases with amplification	Cases with mutations	Protein change
High grade serous ovarian cancer (HGSOC)	584	55	53	-	-
Uterine corpus endometrial carcinoma	529	23	15	7	R53H, I109M, R108H, S127L, D129Y, S15Lfs*5, E76D
Lung squamous cell Carcinoma	487	36	33	3	V121L, C19S, M64I
Cervical squamous cell carcinoma	297	12	11	1	S134L
Pancreatic adenocarcinoma	184	13	13	-	-

Table 1: *LGALS13* gene modifications in cancer (based on TCGA PanCan 2018).

that potentially affected PP13 function (Table 1).

Conclusion

Early intervention in PE has improved maternal and fetal outcomes, yet the available tools are still lacking for the effective early detection of pregnant women at high risk of PE development. Early and effective risk stratification will allow researchers to better classify patients with a higher risk of PE development in the appropriate study group. This will be reflected in more effective and efficient therapeutic options, and more precise clinical study results and interpretation. Based on the promising results of PP13 expression in early PE detection, we support additional clinical studies with larger numbers of pregnant women and more controlled individualized maternal risk factors, to establish an early detection module.

Due to the technical difficulties in maternal serum PP13 measurement, many scientists believe that the discovery of several *LGALS13* mutations in PE might encourage genetic testing, which may enhance the accuracy of maternal serum PP13 level as a tool to identify women at high risk of PE. On the other hand, galectins have been extensively studied in tumor development, invasiveness, and metastasis. Malignant cells release galectins that bind other molecules and perturb their adhesion with surrounding cells and extracellular matrix. We also highlighted the presence of different mutations in *LGALS13* in several types of cancer to encourage more revealing studies on *LGALS13* and the role of its product, PP13, in malignancy development and prognosis, especially in lung, breast, and ovarian cancer.

Disclosure of Interests

None declared. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to Authorship

The article was written by AY. LH helped conceive the article and reviewed the final draft. IC conceived the article, edited all drafts, and reviewed the final draft.

Details of Ethics Approval

Not applicable.

Funding

IC is recipient of Ann and Sol Schreiber OCRA and Liz Tilberis OCRA awards, the Marsha Rivkin Ovarian Center Pilot Award, and WeRoc Research grant from Foundation for Women's Cancer.

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Volume 8 Issue 11 November 2019

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