Inflammatory Markers and Preeclampsia
A Systematic Review

Kathleen Darrah Black ▼ June Andrews Horowitz

Background: Preeclampsia (PE), a serious and variable pregnancy complication affecting 5%–10% of the obstetric population, has an undetermined etiology, yet inflammation is concomitant with its development, particularly in relation to endothelial dysfunction.

Objective: The purpose of this systematic review was to examine the published evidence concerning an association between PE and inflammatory markers for their usefulness in the prediction or early identification of women with PE in antepartum clinical settings.

Methods: In this systematic review, we used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The Cumulative Index for Nursing and Allied Health and MEDLINE/OVID were the electronic databases used for identifying published articles. We placed no time limit on the publication year.

Results: The search generated 798 articles. After removing duplicates, screening abstracts, and conducting full-text reviews, we retained 73 articles and examined 57 unique markers. This review shows that C-reactive protein and the cytokines, specifically the proinflammatory markers IL-6, IL-8, and tumor necrosis factor alpha, garner the most support as potential inflammatory markers for clinical surveillance of PE, particularly during the second and third trimesters.

Discussion: Based on this review, we cannot recommend any single inflammatory marker for routine clinical use to predict/identify PE onset or progression. Research is recommended to examine a combination panel of these four inflammatory markers both with and without clinical risk factors toward the goal of translation to practice.

Key Words: inflammatory • preeclampsia • pre-eclampsia • review

Nursing Research, May/June 2018, Vol 67, No 3, 242–251

With an incidence of 5%–10%, preeclampsia (PE) is a common multisystem pregnancy complication (Harmon et al., 2016). PE is a leading cause of maternal mortality due to organ complications, eclampsia, and cerebral vascular accidents, as well as significant infant adverse outcomes, including intrauterine growth restriction, iatrogenic prematurity, and stillbirth (U.S. Preventative Services Task Force [USPSTF], 2017).

Decades of research into the origins of PE, although fruitful, have resulted in an incomplete understanding of its etiology. What is known is that PE originates with the placenta, and its only cure rests with placental removal upon delivery. Although pregnancy itself is considered a low-grade systemic inflammatory condition, inflammation is further exaggerated in PE because of ineffective placentation and, as such, plays a prominent role in its pathophysiology (Staff et al., 2013).

In the early weeks of normal pregnancies, fetal trophoblasts invade the maternal spiral arteries of the uterine decidua, remodeling them from narrow muscular vessels into wide, flaccid pathways for maximum blood flow for a healthy placenta (Sircar, Thadhani, & Karumanchi, 2015). During the placental stage of pregnancies destined for PE, the trophoblasts invade only superficially, resulting in hypoperfusion of the placenta and hypoxia (Jadli et al., 2015). The second stage of PE presents after 20 weeks of gestation when placental hypoxia results in placental ischemia, oxidative stress, and the release of placental microparticles into the maternal circulation. The cascade continues by causing endothelial activation, release of coagulation proteins, activated immune cells and proinflammatory cytokines, and, consequently, the presence of maternal signs and symptoms of PE (Harmon et al., 2016; Staff et al., 2013).

DIAGNOSIS, CLASSIFICATION, AND SCREENING

According to guidelines from the American College of Obstetricians and Gynecologists (ACOG), PE is diagnosed by the presence of new onset hypertension and proteinuria after 20 weeks of gestation. In the absence of proteinuria, PE may be diagnosed if hypertension is accompanied by signs of liver, pulmonary, cerebral, renal, or coagulation dysfunction (ACOG, 2013). Previously, several clinical guidelines included the categories of "mild" and "severe" PE; however, ACOG (2013) discourages the classification of "mild PE," as PE is progressive

Kathleen Darrah Black, PhD, MSN, RNC-OB, is Adjunct instructor, College of Nursing, Thomas Jefferson University, Philadelphia, Pennsylvania.
June Andrews Horowitz, PhD, RN, PMHCNS-BC, FAAN, is Associate Dean for Graduate Studies and Research & Professor, University of Massachusetts Dartmouth.

DOI: 10.1097/NNR.0000000000000285

and may change immediately after diagnosis, rendering the label inaccurate. Severe PE diagnosis is retained as systolic blood pressure (BP) of 160 mm Hg or higher or diastolic of 110 mm Hg or higher on two occasions at least 4 hours apart with or without signs and symptoms of multisystem involvement. PE is further divided into the subclassifications of "early onset" (less than 34 weeks of gestation) and "late onset" (greater than 34 weeks of gestation), with an early-onset PE carrying additional maternal and fetal risk for adverse outcomes (von Dadelszen, Magee, & Roberts, 2003).

ACOG (2015) has suggested that prediction or early detection of PE may allow for closer surveillance and possibly preventive treatment. Prediction of PE through identification of patient risk factors (e.g., age, parity, obesity, smoking, and certain concomitant health conditions), biochemical analysis (including biomarkers), or physical measures has remained elusive (ACOG, 2013). In addition, the USPSTF has determined that adequate evidence exists to support the accuracy of BP as a current, standard measure for the identification and diagnosis of PE after 20 weeks of gestation (USPSTF, 2017). The USPSTF determined that the common practice of obtaining dipstick urine for protein during prenatal visits has a low diagnostic accuracy for evaluating the amount of proteinuria and therefore does not support this point of care testing for PE. To date, other than BP measurement, no other screening measure independently demonstrates effectiveness as a screen for PE, prompting the USPSTF to recommend investigation of screening algorithms arising from a more complete understanding of its etiology using methodology that can be useful in clinical settings. Thus, lack of effective prediction/screening measurement for PE is a gap in knowledge.

ROLE FOR INFLAMMATORY MARKERS IN THE CLINICAL CARE OF WOMEN WITH PE

Research into the pathophysiology of PE has led to the discovery of changes in levels of circulating factors released during the course of preeclamptic pregnancies. Inflammatory, antiangiogenic, and oxidative stress biomarkers, alone or in combination, have become potential predictive markers of PE as well as potential "therapeutic targets" for interventions at both stages of the disease process (Jadli et al., 2015, p. 190).

Although several categories of potential markers exist, inflammatory markers have been extensively studied over the last several decades. Prior systematic reviews have focused exclusively on a few markers: tumor necrosis factor alpha (TNFα), IL-6, IL-10, and C-reactive protein (CRP) (Lau et al., 2013; Rebelo et al., 2013; C. Xie, Yao, Liu, & Xiong, 2011). In addition, a preponderance of other inflammatory makers has been examined. Kenny et al. (2014) postulated that early identification of PE may not lie with a single marker but perhaps with a combination of markers in conjunction with identification of clinical risk factors. Therefore, a broad examination of inflammatory markers in PE is warranted.

PURPOSE

The purpose of this systematic review was to examine the published evidence concerning an association between PE and inflammatory markers to aid in prediction or screening/early identification of PE and ultimately, timely intervention to prevent PE complications.

METHODS

To conduct this review, we used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009). The Cumulative Index for Nursing and Allied Health and MEDLINE/OVID were the electronic databases used for identifying published articles that met our inclusion criteria. Inclusion criteria were as follows: original research that focused on PE and inflammatory markers, data collection during pregnancy, maternal serum as a source of data, publication in English, and in vivo data collection from humans. Exclusion criteria were as follows: non-English publications, postpartum data only, placental data only, review articles or editorials, nonhuman subjects, and investigations of PE with coexisting condition(s). Although we realized that changes in methodology over time, such as diagnosis and laboratory procedures, may have to be addressed, we placed no time limit on the publication year in order to obtain the full scope of research into inflammatory markers. Search terms (key words and medical subject headings [MeSH] terms) were preeclampsia (and pre-eclampsia) and inflammatory.

Process for Study Selection

After conducting the electronic searches, we identified 798 possible articles for review. After electronic review to remove duplicates, we retained 751 articles. We reviewed titles and abstracts, extracted key items, and removed any remaining duplicates to identify 83 articles for full-text review. We divided the 83 selected articles between coauthors and conducted a full-text review that included extraction of key items for reporting in table of evidence summary forms. The key items were authors/title, year, sample, design and methods, inflammatory markers, findings, and quality rating based on the Johns Hopkins quality rating (i.e., high, good, low quality) rubric for scientific evidence. This quality rating rubric is based on judgment of key elements of scientific rigor, such as methodology quality including degree of control, sampling and sample size, interpretations, and recommendations (Poe & White, 2010). With close inspection, we removed eight additional articles as duplicates that we missed during the initial review and electronic duplicate search. For example, minor differences in reporting identifiers such as authors' initials across databases or journals sometimes resulted in missed duplicates. We dropped two additional articles during

data extraction based on careful consideration of our criteria. For final inclusion and validation, we reviewed the table of evidence summary forms for every article and reviewed articles again whenever a question arose about inclusion. We achieved consensus for each retained study and reached a total of 73 for inclusion. Figure 1 provides the PRISMA flow diagram.

For analysis, we entered data into an SPSS 24 database containing key items: study year, design type, markers studied, laboratory analysis method, trimester of marker analysis, diagnostic criteria used, comparisons done, and major findings for each study. For each marker, our analysis strategy for comparing study results included categorizing the number of significant versus nonsignificant and, when significant, noting the direction (increased vs. decreased). For this review, given the large number of studies and scope of markers identified, we limited our report of detailed findings to markers examined in greater than 10 studies.

FINDINGS

This review includes a variety of inflammatory marker groups: cytokines, systemic acute phase protein (CRP), cell adhesion molecules, cell surface protein markers, and others. Throughout this study, we reviewed 57 unique markers for their association with PE. Many were studied only once, and several markers were the focus of only a few studies with inconsistent findings. Table 1 displays the markers that we examined in this review and their categories. From this comprehensive list, eight markers were given more intense scrutiny. Table 2 specifies the markers, their categories, functions, significance, and direction of change.

The review had no time limit for publication. The first study identified was published in 1958, and the final study was published in December 2016. From the original search total of 798, 73 articles were selected for this review, ranging in time from 1998 through 2016. The reviewed articles ranged from A to B on the John Hopkins Quality Rating Scale, indicating adequacy. Regardless of the year of the study, all but a few of the articles used the BP parameters of diagnosis consistent with the current guidelines from ACOG (2013), that is, onset of elevated BP of greater than or equal to 140/90 on two or more occasions after 20 weeks of gestation. These guidelines have been in place for several decades. Unlike the current guidelines listed earlier, the diagnosis of PE in the studies in this review depended on the inclusion of proteinuria. Because it is a recent change to diagnose PE even in the absence of proteinuria, it is not surprising that only one study included the new diagnostic guidelines (Yildirim et al., 2016). In a few of the

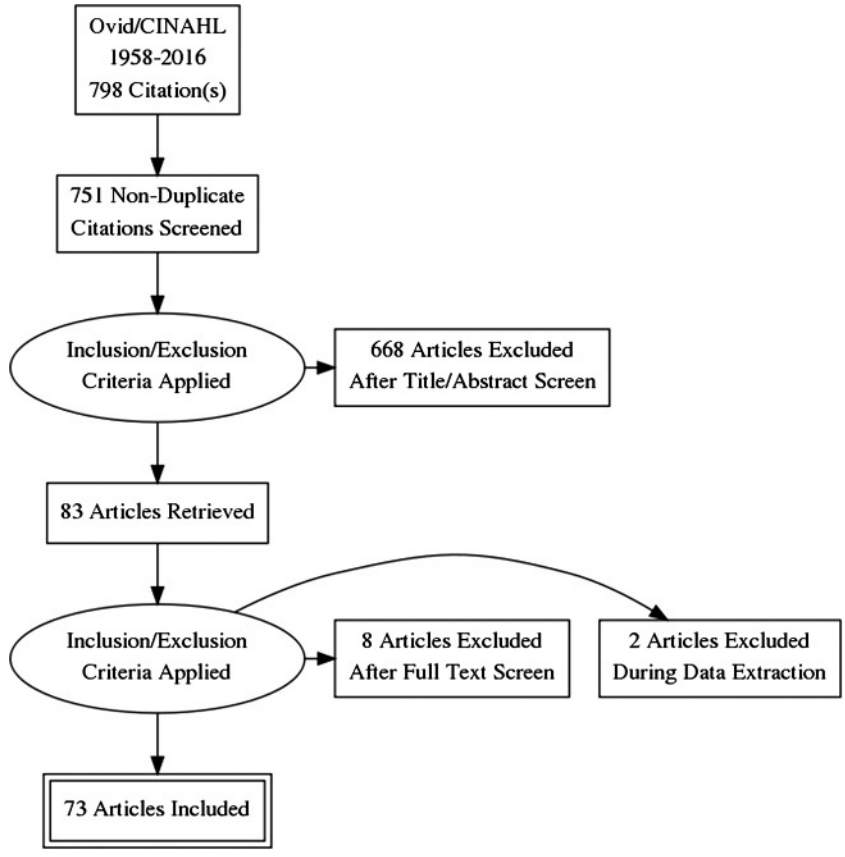

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram for systematic review.

TABLE 1. Classifications of Inflammatory Markers Reviewed

Cytokine	Acute phase protein	Chemokine	Cell adhesion molecule	Cell surface protein	Other
IL-1 RA, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-12p40 subunit, IL-13, IL-15, IL-16, IL-17, IL-18, IL-35, TNFα, GM-CSF, INFγ, leptin, TNFβ, pentraxin 3, TGFβ, CCL2, CCL3, CCL17, CXCL10, CXCL11	CRP	CCL2, CCL3, CCL17, CXCL10, CXCL11, MIP1β	ICAM1, ICAM3, E-selectin, L-selectin, VCAM1	ICAM1, ICAM3, E-selectin, L-selectin, VCAM1, CD4, CD8, CD11b, CD49d, CD55, CD64, CD88	Natural killer cells, YKL40, TLR2, cryoprin, neopterin, calprotectin, procalcitonin, SAA, LMW adenopoectin, MMW adenopoectin, HMW adenopoectin, AAT, sRAGE, Axl receptor tyrosine kinase

Note. IL-1 RA = interleukin 1 receptor antagonist; TNF = tumor necrosis factor; GM-CSF = granulocyte-macrophage colony stimulating factor; CCL2 = C-C motif ligand 2; CXCL10 = C-X-C motif chemokine 10; ICAM1 = intercellular adhesion molecule 1; VCAM1 = vascular cell adhesion molecule; CD4 = cluster of differentiation 4; YKL40 = chitinase-3-like protein (CHI3L1); TLR2 = toll-like receptor 2; SAA = serum amyloid A protein; LMW adenopoectin = low molecular weight adenopoectin; MMW adenopoectin = medium molecular weight adenopoectin; HMW adenopoectin = high molecular weight adenopoectin; AAT = alpha-1 adiponectin; sRAGE = serum receptor advanced glycation end product; MIP1 = macrophage inflammatory protein 1.

studies, only the diagnosis of PE was listed, rather than specific parameters of BP or proteinuria. In studies investigating mild and severe PE, the researchers distinguished between the two by defining severe PE when BP met or exceeded 160/110 on two consecutive occasions with proteinuria or when evidence of multisystem involvement was present. In most of the studies in this review, urine dipstick for measurement of proteinuria was also used as a PE indicator.

Laboratory analysis varied throughout the research. The ELISA and multiplex arrays were the most commonly used techniques used to measure inflammatory markers. Considered a sensitive measure, ELISA is referred to as the "gold standard," but more recently, multiplex arrays are being used as they can measure multiple biomarkers simultaneously and demonstrate similar performance capabilities (Salisbury & Bronas, 2014). Other researchers for studies reviewed described a multistep process of measurement without the use of commercial products, making comparisons between techniques difficult.

All but a few of these studies examined were case–control, retrospective studies comparing levels of inflammatory biomarkers between women with normotensive pregnancies and those with PE. In most of these studies ($n = 58$), blood samples were taken from pregnant women in their second or third trimesters, when PE is clinically diagnosed. Researchers in a few retrospective cohort studies used secondary analyses of earlier prospective studies by examining previously obtained blood samples from the first half of pregnancy (Gammill et al., 2010; Haedersdal et al., 2013; Siljee et al., 2013; Taylor et al., 2016). Only two studies used a stronger prospective design by examining biomarkers in pregnant women during the first half of pregnancy (Carty et al., 2012; Hung et al., 2012).

SELECTED INFLAMMATORY MARKERS

IL-1β (Proinflammatory Cytokine)

In 15 case–control studies, researchers examined IL-1β, an inflammatory cytokine, as a marker for PE (Bernardi, Guolo,

TABLE 2. Listing of Most Studied Inflammatory Markers

Biomarker	Classification	Inflammatory response	No. of times studied	No. of studies: Significantly higher in preeclampsia than normal pregnancies	No. of studies: Significantly lower in preeclampsia than normal pregnancies	No. of studies: Nonsignificant findings
IL-1β	Cytokine	Proinflammatory	15	6	1	8
IL-2[a]	Cytokine	Proinflammatory	11	6	0	4
IL-6	Cytokine	Proinflammatory	28	21	0	7
IL-8	Cytokine	Proinflammatory	12	8	0	4
IL-10	Cytokine	Anti-inflammatory	18	4	4	10
INFγ	Cytokine	Proinflammatory	17	6	2	9
TNFα	Cytokine	Proinflammatory	25	18	0	7
CRP	Systemic acute phase protein	Proinflammatory	18	13	0	5

Note. IL-1β = inteleukin-1β; INFγ = interferon γ; TNF = tumor necrosis factor; CRP = C-reactive protein.
[a]Taylor et al. (2016) reported undetectable levels.

Bortolin, Petronilho, & Dal-Pizzol, 2008; Boij et al., 2012; Carty et al., 2012; Conrad, Miles, & Benyo, 1998; Daneva, Hadži-Lega, & Stefanovic, 2016; Ferguson, McElrath, Chen, Mukherjee, & Meeker, 2014; Jonsson et al., 2006; Kalinderis et al., 2011; Luppi & Deloia, 2006; Molvarec et al., 2011a; Montagnana et al., 2008; Pinheiro et al., 2013; Siljee et al., 2013; Taylor et al., 2016; F. Xie et al., 2010). Of the 15 studies, six reported significantly higher levels of IL-1β in PE pregnancies than controls. In a case–control study, Siljee et al. (2013) performed a secondary analysis of serum blood samples previously drawn in a first-trimester sample of primigravidas and multigravidas and determined that IL-1β is significantly increased in early-onset PE pregnancies (n = 35) when compared to normal pregnancy controls (n = 35). In several case–control studies that used blood drawn in the third trimester, researchers reported significant increases in IL-1β in samples of primigravidas and multiparas (Daneva et al., 2016; Luppi & Deloia, 2006; Kalinderis et al., 2011; Montagnana et al., 2008; F. Xie et al., 2010). In a recent case–control study, Daneva et al. (2016) found a significantly higher concentration of IL-1β in pregnancies complicated by severe PE (n = 25) when compared to normal pregnancies (n = 50); however, when those pregnancies with mild PE (n = 25) were compared to normal pregnancies, the results were insignificant. The researchers concluded that levels of IL-1β increase with the severity of this progressive disease. Conversely, in a large retrospective case study of primigravidas, Taylor et al. (2016) performed a secondary analysis of IL-1β drawn between 9 and 26 weeks. Researchers found that IL-1β maternal serum level was significantly associated with a *decreased* risk for PE both at term and preterm. Taylor et al. (2016) noted that, because this sample had a mean gestational age of 16 weeks, perhaps IL-1β may not be well tolerated in early pregnancy and suggested that further research using IL 1β as a marker in the first trimester may be warranted.

Eight studies remaining showed no significant association between IL-1β and PE. Moreover, Molvarec et al. (2011a) and Pinheiro et al. (2013) suggested that the lack of significance of IL-1β as a marker for PE may be attributed to the short half-life of the cytokine in the maternal circulation, thereby bringing its usefulness as a marker into question.

IL-2 (Proinflammatory Cytokine)

Through 11 studies, researchers examined the usefulness of IL-2 as a marker for PE (Boij et al., 2012; Carty et al., 2012; Daneva et al., 2016; Jonsson et al., 2006; Molvarec et al., 2011a; Sharma, Singh, Trivedi, & Bhattacharjee, 2011a, 2011b; Singh, Sharma, Raghunandan, & Bhattacharjee, 2010; Szarka, Rigo, Lazar, Beko, & Molvarec, 2010; Taylor et al., 2016; F. Xie et al., 2010). In one of these studies, IL-2 was nondetectable in maternal serum (Taylor et al., 2016).

Results of studies examining IL-2 as a marker for PE were mixed. Researchers in six studies determined that IL-2 was significantly higher in pregnancies complicated by PE than in normal pregnancies (Daneva et al., 2016; Molvarec et al., 2011b; Sharma et al., 2011a, 2011b; Singh et al., 2010; Szarka et al., 2010). In a large case–control study of nonsmoker primigravidas in the third trimester, Sharma et al. (2011b) investigated serum IL-2 levels in women with PE (n = 100) and women with normal pregnancies (n = 100) and reported that serum IL-2 levels were significantly higher in women with PE than in controls. The researchers concluded that this association was consistent with PE etiology of endothelial activation and inflammation. When examining women with mild (n = 25) and severe PE (n = 25), Daneva et al. (2016) reported that IL-2 levels were significantly increased in PE when compared to levels in normal pregnancies regardless of disease severity.

In contrast, results of the four remaining studies showed no significant differences in IL-2 between those with PE and normotensive pregnant women in their third trimester. For example, Boji et al. (2012) found no significant difference in IL-2 levels between those with PE (n = 114) and those with normal pregnancies (n = 100); however, this sample of women with PE (approximately 2/3) predominately had mild PE.

IL-6 (Proinflammatory Cytokine)

In *all* of the 21 studies reporting *significant findings*, researchers reported higher levels of IL-6 in pregnancies complicated by PE when compared to normal pregnancies. Taylor et al. (2016) examined IL-6 levels during the second trimester and found that elevated levels of this cytokine predicted term PE. In case–control studies during the third trimesters, researchers reported a significant increase in levels of IL-6 in pregnancies complicated by PE compared to normal pregnancies (Bernardi et al., 2008, 2012; Catarino et al., 2012; Conrad et al., 1998; Daneva et al., 2016; Jonsson et al., 2006; Kalinderis al., 2011; Luppi & Deloia, 2006; Molvarec et al., 2011b; Pinheiro et al., 2013; Sharma, Satyam, & Sharma, 2007; Silva et al., 2013; Singh et al., 2010; Swellam, Samy, Wahab, & Ibrahim, 2009; Szarka et al., 2010; Teran et al., 2001; Toldi, Bíró, et al., 2011; Wang et al., 2011; Xiao et al., 2012; F. Xie et al., 2010). In an example of a study controlled for body mass index (BMI) and smoking, Szarka et al. (2010) examined the levels of IL-6 drawn in the third trimester on a group of women with PE (n = 60) compared to women with normal pregnancies (n = 60). Women with PE experienced significantly higher levels of IL-6 than those women with normal pregnancies, but the researchers reported no differences in IL-6 between those women with PE based on severity or timing of onset of disease. When disease severity was considered, results were mixed. F. Xie et al. (2010) and Pinheiro et al. (2013) found significant increases in IL-6 in women with severe PE as compared to mild PE. In contrast, Daneva et al. (2016) reported significantly higher IL-6 levels in mild PE, but not in severe PE, when compared to normal pregnancies. Silva et al. (2013) found no

significant difference between groups according to severity. In addition, seven studies reported no significant differences in IL-6 levels between pregnancies complicated by PE and normal pregnancies (Al-Othman, Omu, Diejomaoh, Al-Yatama, & Al-Qattan, 2001; Boij et al., 2012; Carty et al., 2012; Montagnana et al., 2008; Ozkan et al., 2014; Taylor et al., 2016; Vitoratos, Economou, Iavazzo, Panoulis, & Creatsas, 2010). Taylor et al. (2016) found elevation for PE at term only.

IL-8 (Proinflammatory Cytokine)

Of the 12 case–control studies examining IL-8 as a marker for PE, eight demonstrated that IL-8 was significantly increased in PE when compared to normal pregnancies (Cemgil Arikan, Aral, Coskun, & Ozer, 2012; Jonsson et al., 2006; Luppi & Deloia, 2006; Molvarec et al., 2011a; Pinheiro et al., 2013; Sahin et al., 2015; Sharma et al., 2007; Szarka et al., 2010). Pinheiro et al. (2013) examined serum samples from women with severe PE (n = 69) comparing to women with normal pregnancies (n = 69) during the second and third trimesters and found that IL-8 levels were significantly higher in those women with PE. Sahin et al. (2015) reported that IL-8 was significantly higher in those women diagnosed with severe PE (n = 23) when compared to a control group with normal pregnancies (n = 80) in the third trimester; however, no significant difference was reported between those women with mild PE (n = 18) and normal pregnancies. However, BMI could be a confounding variable, as it was higher in women with PE. Of interest is that *no* study reported an association between *decreased* IL-8 and PE.

Conversely, four studies demonstrated insignificant findings (Boij et al., 2012; Carty et al., 2012; Daneva et al., 2016; Taylor et al., 2016). Notably, two studies drew samples from women in their first and second trimesters (Carty et al., 2012; Taylor et al., 2016).

IL-10 (Anti-inflammatory Cytokine)

Of the 18 studies included in this review, four case–control studies in the third trimester determined that IL-10 levels were lower in pregnancies complicated with PE compared to normal pregnancies (Pinheiro et al., 2013; Sahin et al., 2015; Sharma et al., 2007; F. Xie et al., 2010). F. Xie et al. (2010) reported that IL-10 levels were significantly lower in women with PE (n = 50) than in normal pregnancy controls (n = 75). Researchers concluded that this finding was consistent with the previous research on this cytokine. In contrast, four case–control studies showed significantly increased levels of IL-10 in pregnancies with PE when compared to normal pregnancies in the third trimester (Ferguson et al., 2014; Molvarec et al., 2011a; Silva et al., 2013; Szarka et al., 2010). For example, Silva et al. (2013) examined levels of IL-10 in the third trimester and found increased levels in women with both mild (n = 17) and severe PE (n = 23) when compared to normal pregnant women (n = 50), leading the researchers to suggest that increases in IL-10 may be compensatory in PE.

Ten case–control studies showed no significant differences in IL-10 levels between those women with PE and normal controls (Bachmayer, Rafik Hamad, Liszka, Bremme, & Sverremark-Ekström, 2006; Bernardi et al., 2008; Boij et al., 2012; Carty et al., 2012; Conrad et al., 1998; Daneva et al., 2016; Jonsson et al., 2006; Makris, Xu, Yu, Thornton, & Hennessy, 2006; Ozkan et al., 2014; Taylor et al., 2016). Although Daneva et al. (2016) found no difference between women with PE and normal pregnancy controls, the researchers found that there was a significant increase between those diagnosed with mild PE compared to those with severe PE.

Interferon γ (Proinflammatory Cytokine)

Interferon γ (INFγ) was examined in 17 studies identified in this review. Of those studies, findings in nine were nonsignificant (Boij et al., 2012; Carty et al., 2012; Cemgil Arikan et al., 2012; Haedersdal et al., 2013; Jonsson et al., 2006; Montagnana et al., 2008; Taylor et al., 2016; Vitoratos et al., 2010; F. Xie et al., 2010), six showed higher findings for PE (Ozkan et al., 2014; Pinheiro et al., 2013; Molvarec et al., 2011a; Sharma et al., 2011a, 2011b; Szarka et al., 2010), and two showed lower levels for PE (Bueno-Sánchez et al., 2014; Giurgescu et al., 2015). The mixed results call for an examination of selected studies to draw conclusions about results. In examining INFγ levels in PE (n = 40) and normotensive pregnancies (n = 40), Ozkan et al. (2014) reported that INFγ was higher in PE. The authors concluded that "increased INF gamma/TGF beta production in PE may lead to less cytokine inhibitory activity in PE which may account for increased proteinuria and blood pressure" (p. 1516). This result, in conjunction with other results in this review, suggests a complex interactive process among inflammatory markers in PE. In contrast, results from another study showed *lower* INFγ among women with PE (n = 12) versus normal pregnant controls (n = 37; Giurgescu et al., 2015).

Tumor Necrosis Factor Alpha

Researchers have widely investigated TNFα in PE through 25 identified studies. Results were somewhat mixed with nonsignificant findings in seven studies (Artunc-Ulkumen, Guvenc, Goker, & Gozukara, 2015; Boij et al., 2012; Carty et al., 2012; v Jonsson et al., 2006; Montagnana et al., 2008; Ozkan et al., 2014; Pinheiro et al., 2013) and significantly higher findings in PE in 18 studies (Bernardi et al., 2008; Bueno-Sánchez et al., 2014; Cackovic et al., 2008; Catarino et al., 2012; Conrad et al., 1998; Ferguson et al., 2014; Hou, Zhu, Ma, Li, & Zhang, 2012; Luppi & Deloia, 2006; Molvarec et al., 2011a; Sharma et al., 2007, 2011a, 2011b; Silva et al., 2013; Singh et al., 2010; Szarka et al., 2010; Teran et al., 2001; Vitoratos et al., 2010; F. Xie et al., 2010). Notably, *no studies showed lower TNFα* associated with PE. One prospective longitudinal

study (Carty et al., 2012) illustrates well-designed research that produced nonsignificant results for TNFα in relation to PE. From a population of 2,600 pregnant women at 12–16 weeks of gestation, researchers identified a subsample of women with risk factors for PE to sample again at gestational weeks 16 and 28 (11 cases, 39 controls). Results showed no significant difference for TNFα between groups, leading researchers to question the sensitivity of the multianalyte biochip array used to analyze this marker. Interestingly, other researchers (Conrad et al., 1998) examined TNFα concentrations using ELISA methodology in women with PE (n = 27) and normal pregnancy (n = 29). In sharp distinction to results of the previous study, their findings demonstrated a three times higher median concentration for women with PE compared to normal controls in the third trimester.

C-Reactive Protein

CRP is another widely studied inflammatory marker in PE. We identified 18 studies in this review. Results from 13 studies (Belo et al., 2003; Braekke, Holthe, Harsem, Fagerhol, & Staff, 2005; Can et al., 2011; Catarino et al., 2012; Cemgil Arikan et al., 2012; Fialova et al., 2004; Kronborg et al., 2007; Kucukgoz Gulec et al., 2012; Swellam et al., 2009; Teran et al., 2001; Toldi, Rigó, Stenczer, Vásárhelyi, & Molvarec, 2011; Tuuri, Jauhiainen, Tikkanen, & Kaaja, 2014; van Rijn et al., 2014) indicated significantly higher CRP levels for women with PE compared to controls. In a study of CRP and PE, Fialova et al. (2004) followed 10 women with PE and 11 women with normal pregnancies in the third trimester of pregnancy. CRP for women with PE was significantly increased in comparison with third trimester levels for women with normal pregnancy. However, in five other studies, findings were nonsignificant (Ferguson et al., 2014; Haedersdal et al., 2013; Savvidou, Lees, Parra, Hingorani, & Nicolaides, 2002; von Versen-Hoeynck, Hubel, Gallaher, Gammill, & Powers, 2009). Notably, *no studies showed significantly lower* results for CRP with PE.

Strengths and Limitations

Strengths of this systematic review were the use of PRISMA guidelines as an organizing framework for the review, comprehensive inclusion criteria to avoid premature closure, and coauthor consensus on extracting data and summarizing findings, thus increasing validity and reliability of the study. Overall quality of studies reviewed was evaluated as good (i.e., ratings were A/B). Nonetheless, some nonsignificant results may be artifacts of small sample sizes. However, we acknowledge the challenges inherent in studying low prevalence conditions like PE that typically yield small samples. A preponderance of the studies we reviewed used case–control, retrospective designs; few were prospective beginning in the first trimester. Prospective studies require a very large sample to accrue the numbers of women who eventually develop PE; again, this is a limitation in low-prevalence conditions. Most of the studies controlled for age, parity, and gestational age at the time of data collection. Possible explanations for mixed results among the markers included in this review include methodological variation in the timing of measurement (first, second, or third trimesters); characteristics of control participants such as BMI, smoking, and intrauterine growth restriction; and early/late onset of PE, severity of PE, and sensitivity of the assays performed.

Discussion and Conclusions

In this systematic review, we chose to include studies involving a wide range of inflammatory markers. Our overarching aim was to determine if we could identify inflammatory markers as predictors/indicators of PE based on the available evidence. Examination of 73 studies published from 1998 to 2016 revealed that a handful of inflammatory markers, that is, IL-6, IL-8, TNFα, and CRP, may prove useful in identifying pregnant women at risk for developing PE. In systematic reviews, both Lau et al. (2013) and C. Xie et al. (2011) found that TNF, IL-6, and IL-10 were elevated in studies of PE. Similarly, we determined that TNF and IL-6 were meaningful markers, but not IL-10. Our investigation revealed conflicting results for IL-10: four studies demonstrated a significantly lower level of this marker in women with PE, whereas three showed significantly higher results. Most of the studies had no significant findings. As a result, we did not include IL-10 as a suggested marker for PE. Notably, in a meta-analysis, Rebelo et al. (2013) reviewed seven studies for the association of CRP as a marker for PE and found that elevated CRP was associated with PE. Similarly, based on this review, we conclude that CRP is a potential clinical marker. In addition to the previously identified markers, we recognize the potential of IL-6 as a marker for PE, given the number of studies reporting a significantly higher level in PE than in normal pregnancies. Moreover, no individual inflammatory marker emerged as a strong single predictor/indicator of PE. A few frequently studied markers thought by various researchers to have good promise as indicators of PE risk proved disappointing. Specifically, results for IL-1β, IL-10, and INF showed nonsignificance and/or mixed results in many studies and therefore are not recommended for inclusion as potential clinical markers.

RECOMMENDATIONS

Based on the evidence from this systematic review, our primary recommendation is to pursue additional research using the following inflammatory markers IL-6, IL-8, TNFα, and CRP that were shown to be significant and consistent predictors of PE, particularly in the second and third trimesters when the preponderance of studies reviewed was conducted. Research examining the effectiveness of these biomarkers as a panel alone or in conjunction with known clinical risk factors, such as elevated BMI, hypertension, age, smoking status, and medical history, may prove useful in an effort to create a predictive model of PE in prenatal clinical settings. Should

future research support the efficacy of these markers as PE predictors/identifiers, using a panel of biomarkers is likely to be a cost-effective and viable approach for identifying PE risk/progression. Once a panel for inflammatory markers is established and examined for its predictive ability alone or with other clinical features, translation to practice becomes possible as part of standard prenatal monitoring.

Accepted for publication February 1, 2018.

The authors thank Malinda Hawkins, RN, BSN, Penn Medical Dermatology, for abstract review assistance and Patricia Wynne, MS, Library Information Services, Thomas Jefferson University, for library assistance.

The authors have no conflicts of interest to disclose.

Corresponding author: Kathleen Darrah Black, PhD, MSN, RNC-OB, College of Nursing, Thomas Jefferson University, 130 S. Ninth St., Philadelphia, PA 19107(e-mail: kathleen.black@jefferson.edu).

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