

Novel biomarkers in the differential diagnosis of preeclampsia and lupus flare in pregnancy

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ABSTRACT

Preeclampsia and systemic lupus erythematosus are medical conditions with established elevated risks of pregnancy complications and fetal compromise. Active lupus during pregnancy can trigger the appearance of preeclampsia. Research has demonstrated an increase in lupus disease flares during pregnancy, secondary to hormonal shifts required in order to maintain pregnancy. Hemolytic anemia, leucopenia, thrombocytopenia, sudden onset of hypertension after 20 weeks of gestation and decreasing complement components such as C3, C4 and CH50 are hallmarks of lupus flares during pregnancy. Timely and accurate prediction of preeclampsia is now feasible through estimation of novel placental and endothelial biomarkers, chiefly sFlt-1 and PlGF. A sFlt-1 to PlGF ratio under 38, in patients under 34 weeks of gestation suspected of disease, boasts the highest negative predictive value for preeclampsia and can successfully rule out preeclampsia development in the following 4 weeks in patients with normal values. Moreover, the sFlt-1 to PlGF ratio has proven its utility in the differential diagnosis of preeclampsia and active lupus nephritis, with normal ratio values noted in cases of lupus flares during pregnancy. Further research is required in order to identify other novel potential biomarkers.

Keywords: preeclampsia, systemic lupus erythematosus, lupus flare, lupus nephritis, high-risk pregnancy, novel biomarkers, pregnancy, sFlt-1, PlGF

INTRODUCTION

Whilst both systemic lupus erythematosus (SLE) and preeclampsia (PE) are defined as systemic entities with significant neonatal and maternal morbidity and mortality rates and generally display similar signs and symptoms, timing of clinical onset of disease, accompanied by alterations in specific blood work and urine tests facilitate the differential diagnosis of preeclampsia and lupus flares in pregnancy. Novel biomarkers (PlGF, sFlt-1, PP13, sENG, ADMA, adipsin etc.) further support this endeavor and constitute a research priority for obstetricians worldwide, since flares of lupus activity during pregnancy, onset of PE, preterm birth, intrauterine growth retardation and fetal mortality are well-documented risks of SLE and PE. Due to ongoing research and medical progress, pregnancy in both systemic lupus erythematosus and preeclampsia have favorable outcomes in most cases.

MATERIALS AND METHODS

Systematic review of English literature using PubMed, Medline, and Google Scholar databases was conducted. Patient-specific cohort studies were identified by using the following search criteria: “pregnancy”, “preeclampsia”, “lupus in pregnancy”, “systemic lupus erythematosus”. Inclusion criteria further included journal articles that noted novel biomarkers and differential diagnosis methods of preeclampsia and lupus flares in pregnancy. Non-English language articles and studies/trials not conducted on humans were excluded. No limitations were placed on geographical location, race, maternal or gestational age.

PREECLAMPSIA

Preeclampsia is a systemic condition that affects up to 5% of pregnancies worldwide and is associated with considerable maternal and neonatal morbidity and mortality [1]. Therapeutic options are limited,

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the only cure is delivery, either at term (in cases of mild forms) or pre-term (if maternal organ failure or seizures are present). In order to lower such risks, timely and proper management of PE represent key aspects of antenatal care [2,3]. Despite being a leading cause of maternal death worldwide, pathophysiology of PE and its exact mechanisms remain unknown and have been considered a priority for research in many guidelines, as it would ensure proper and effective use of risk-based prenatal care resources, targeted surveillance and timely delivery. According to the gestational age at clinical diagnosis, PE is classified in: early-onset preeclampsia (diagnosed before 34 weeks of gestational age, considered to be triggered by improper invasion of the trophoblast of the maternal spiral arteries), and late-onset preeclampsia (diagnosed after 34 weeks of gestation, determined by maternal cardiovascular disorders or co-existing comorbidities). Additional subtypes of PE have been described according to various etiologies or pathobiological mechanisms [4].

Preeclampsia screening methods

In order to improve preterm PE risk prediction, especially in nulliparous women that do not present overt risk factors, a first trimester screening algorithm has been developed. Maternal characteristics, blood pressure, obstetric and general medical history should be accompanied, where possible and available, by uterine artery Doppler measurements and biomarker evaluation [5-7]. In cases of suspected preterm PE, biomarkers such as placental growth factor (PIGF) and soluble fms-like tyrosine kinase 1 (sFlt-1), pro- and anti-angiogenic factors respectively, have proven to be clinically useful, with high negative predictive value. Consistent efforts have been made for the identification of potential novel biomarkers originating from the main organs involved in the pathophysiology of PE (cardiovascular, placental and urinary biomarkers) [8], as well as broader screening methods such as the use of omics (epigenetics, transcriptomics, proteomics and metabolomics). Despite recent progress, there are currently no reliable biomarkers noted in literature for the identification of women at high risk of developing PE at term [8].

Placental insufficiency and endothelial dysfunction have been indicated as key factors in developing PE. As such, biomarkers indicating placental or endothelial dysfunction have been studied.

Placental RNAs have been identified in the maternal circulation during pregnancy and have been proven to be cleared shortly postpartum [9,10]. Disruptions in the placental mRNA, miRNA, circular and long-non coding RNA have been studied in both healthy and preeclamptic patients. Altered expression of circulating mRNAs (such as adrenomedullin

[11], Hoxb3, NR4A2, EMP1, PGM5, AKIL, UGT2B1) were noted in cases of pregnant women with severe placental insufficiency at risk of imminent stillbirth [12]. Chromosome 19 miRNA cluster (C19MC) is composed of 56 mature miRNA found in embryonic cells and the placenta. Combination of miR520a-5p, miR-517-5p and miR-525-5p boast high predictive values for late-term PE (sensitivity 44%, specificity 90%) [13]. However, research evaluating the actual potential of these molecules is scarce and the population studied is limited.

Placental proteins originating from the placental trophoblast such as PIGF and sFlt-1, proangiogenic and antiangiogenic biomarkers respectively, are used in the prediction of early-onset and preterm PE (diagnosed at 37 weeks of gestation or less). In healthy pregnancies, PIGF levels decrease after 30 weeks of gestation, whilst sFlt-1 levels increase after 30 to 32 weeks of gestation [14-17]. Since placental dysfunction seems to be a minor component in the development of late onset PE, use of PIGF, sFlt-1 and sFlt-1 to PIGF ratio is not recommended [18].

Placental Growth Factor (PIGF) remains the best studied biomarker in PE. Current research has shown that women who are predisposed to develop preterm PE generally have lower levels of PIGF, due to placental insufficiency [5,17,19-21]. As such, PIGF has demonstrated increased risk prediction potential for the development of preterm PE, when used alongside clinical examination and patient history. With a high negative predictive value, PIGF levels under 100 pg/ml in women at less than 35 weeks of gestation suspected of preterm preeclampsia have proven superior to commonly used clinical tests (blood pressure, liver or urine tests) in ruling out severe preeclampsia requiring delivery within two weeks [22]. It must, however, be noted that PIGF levels vary according to gestational age and in a low risk population without clinical suspicion of disease, estimation of PIGF levels has not been proven to be clinically useful [8].

Soluble fms-like tyrosine kinase-1 (sFlt-1) is an antiangiogenic placental protein, with at least two splice variants, pursuant to RNA expression: sFlt1-1, sFlt1_v1, sFlt1-i13 and sFlt1-14, of which sFlt1-14 is a highly specific placental biomarker strikingly elevated in preeclamptic patients [23].

According to the PROGNOSIS study, an sFlt-1 to PIGF ratio of less than 38 holds a negative predictive value of over 99% and can thus successfully rule out the likelihood of developing PE in the following seven days in women at less than 37 weeks of gestation suspected of developing PE [14]. When the ratio exceeds 38, the positive predictive value of developing PE within one month is approximately 37% and has a sensitivity of around 66% [14]. Both the sFlt-1 to

PIGF ratio and PIGF alone have proven similar high negative predictive values in ruling out early-onset PE in women with normal results [8].

Dilinoleoyl-glycerol (DLG) is a more recently discovered biomarker that, when used in combination with PIGF, in patients at 15 weeks of gestation, effectively predicted increased risk of preterm PE. Insulin resistance is a common trait found in PE. Increased levels of intracellular diacylglycerol concentrations lead to the activation of new protein-kinase C which, in turn, inhibits insulin action in the skeletal muscle and in the liver [24]. Common metabolic alterations occurring in pregnancy, such as transient insulin resistance, increased coagulation and hyperlipidemia are augmented in PE, therefore measurement of DLG levels must be employed in order to accurately reflect the risk of developing PE secondary to patient disposition for metabolic syndrome [25-27].

Heptadecanoyl-2-hydroxy-sn-glycero-3-phosphocholine (1-HGP) is a biomarker related to endothelial dysfunction and vascular inflammation. Measurement of 1-HGP levels in pregnant patients expanded the risk prediction potential for any form of PE development, since its hydrolyzed form (lysophosphatidic acid, LPA) is a potent mediator of the immune response and could be involved in improper upregulation of inflammatory cytokine production [4], secondary to placental ischemia and strong pro-inflammatory tendency found in PE [4].

Use of PIGF, DLG and 1-HGP have thus been proposed as a risk prediction test in the IMPROVED study [28]. According to current research, use of PIGF alongside DLG has improved the sensitivity for preterm PE detection from 48% to 74%, whilst combining 1-HGP with DLG in the second partition improved the preterm PE prediction sensitivity to 78% in nulliparous women without any apparent risk factors [4].

Placental protein 13 (PP13) is derived from the syncytiotrophoblast [29] and plays a key role in the remodeling of maternal arteries and in placentation. In normal pregnancies, levels of PP13 gradually increase, whereas in preeclamptic patients, during the first trimester, disproportionately low levels of PP13 were identified [30-32] with a marked increase in the last two trimesters. According to a study developed by Nicolaidis et al. [33], estimation of serum PP13 levels and measurement via Doppler ultrasonography of the maternal uterine artery pulsating index can be useful in cases of patients at risk of first trimester PE. PP13 alone has a demonstrated specificity of over 80% and sensitivity of 27%, with a higher negative predictive value when used alongside PIGF or maternal uterine pulsating index during the first trimester [33].

Pregnancy associated plasma protein-A (PAPP-A) originates from the placental trophoblasts and is

screened during the first trimester of pregnancy. It is a key factor in regulating fetal growth.

Alpha fetoprotein (AFP) is screened during the second trimester of pregnancy and is produced by the fetal liver. Whilst both can be used as biomarkers on their own, a combined ratio of AFP to PAPP-A over 10 has proven to detect a relative risk of developing severe PE, with a higher predictive value than either protein alone. It must be noted that PAPP-A is indicated only in cases of suspected risk for early onset PE, in which case levels of PAPP-A are markedly decreased, as compared to late onset PE, where levels of PAPP-A do not differ from those found in a healthy population [33].

Growth Differentiation Factor 15 (GDF-15) derives from the placenta and its production is triggered in inflammation or cellular injury. At 36 weeks of gestation, high levels of GDF-15 were reported. Combined use of placental biomarkers with the sFlt-1 to PIGF ratio delivered improved predictive values [23].

Neutrophil gelatinase associated lipocalin (NGAL or lipocalin-2, uterocalin, siderocalin, 24p3) has increased values in cases of inflammation, infection, cancer, renal or cardiovascular disease and epithelial cell dysfunction. NGAL has been reported as the most timely and accurate indicator of acute kidney damage, with possibility of detection within the first two hours of renal impairment [33]. Taking into account that endothelial injury, inflammation and kidney injury are base traits of preeclampsia, elevated levels of NGAL were reported during the first two trimesters in preeclamptic patients. Thus, estimation of NGAL levels in both early- and late-onset suspected preeclampsia is plausible, though it may require use alongside additional, more specific biomarkers [33].

Recent proteomic studies have indicated that more than 130 urine proteins could improve timely detection of PE [34]. Patients suffering from PE have a different urine proteomic profile compared to healthy, pregnant patients. Changes in the urine proteomic profile may be observed up to 12 weeks before the appearance of clinical signs or symptoms of PE.

Use of *serpin A1* alongside *albumin* proved high accuracy for exposing patients at significant risk of developing PE up to 25 weeks before clinical diagnosis and, thus, indicating severe cases of PE that require immediate delivery [34]. Increased levels of *serpin A1* in urine have been linked to the severity of PE [34]. *Ceruloplasmin* and *serpin A7* were also significantly upregulated at 20-24 and 30-34 weeks of gestation in patients who subsequently developed PE. Ceruloplasmin is a copper-binding protein with antioxidant ferroxidase properties that is upregulated in PE secondary to placental ischemia

[34]. The exact mechanism behind the upregulation of serpin A7 (or thyroxine-binding globulin, TBG) in PE remains unknown [34].

Serpin A5, C3, ALB, TF and HBB represent a group of urine proteomic biomarkers that have shown high potential for timely prediction of PE development [34].

Endothelial RNAs such as *mir-574-5p, mir-1972* and *mir-4793* were reported as elevated in PE. Significantly decreased levels of endothelial miRNAs, such as *miR363* at 28 and 36 weeks of gestation and *miR149, miR424* and *miR18a* at 36 weeks have a modestly-proven predictive potential for term PE. Combined use of *miR363* and *miR149* proved a specificity of 90% and sensitivity of 45% [8].

Endothelial proteins could be potentially useful in detection and risk classification of PE.

Asymmetric dimethylarginine (ADMA) diminishes nitric oxide production and dysregulates vital processes such as vasodilation, platelet aggregation and leukocyte adhesion. It has modest predictive values when identified in patients after 20 weeks of gestation at risk of developing early-onset PE. *Endothelin-1 (ET-1)* is secreted primarily by the endothelial and smooth muscle cells in the vascular system and is involved in vasoconstriction. Estimation of its precursor protein, *CT-pro-ET 1* and *sFlt-1* alongside measurement of systolic blood pressure revealed a 90% specificity and 80% sensitivity in predicting severe preeclampsia within the following week in patients suffering from essential of gestational hypertension, subclinical or moderate PE. *Endocan* and *VCAM-1* were found at increased levels and have a reported modest potential as PE biomarkers [8].

Soluble endoglin (sENG) is a promising and useful biomarker for the severity stratification of disease [35], when found in high levels in the first and second trimesters of pregnancy, around two-to-three months prior to clinical onset of PE. Altered levels of sENG and sFlt-1 from the first to the second trimester of pregnancy accurately predict preterm PE [35]. sENG levels remain elevated in the plasma of preeclamptic patients throughout the entire pregnancy and revert back to normal in the postpartum period. Determination of plasma sENG levels at 11-13 weeks of gestation yields accurate predictive results [33].

Pregnant women with PE present increased levels of plasma *sENG, adipsin* and *C5a* compared to healthy patients, before delivery. Potential diagnostic biomarkers for severe PE include complement proteins such as C1q, Bb and C5b-9) [35].

Upregulation of hCG, creatine, angiogenin, progesterone, TNF, sTNFr-2, TNF-alpha, alanine and phenylalanine and downregulation of glutamine, glycine and glutamate has been identified in women with PE [36].

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a systemic, chronic autoimmune disease pinpointed mainly in women of reproductive age. It is characterized by systemic inflammation with potential lesions identified mainly in the central nervous system, renal system, joints, serous membranes and skin. The clinical course of SLE is represented by fluctuating cycles of disease flares followed by remission. Common laboratory findings in SLE include an association of autoantigens to an array of high titres of autoantibodies. SLE complicates approximately 4500 pregnancies in the USA yearly of which almost 15% develop PE [37].

Flares of lupus disease activity are frequent during pregnancy or immediately after delivery, less so in the third trimester of pregnancy [37]. Hematological and renal flares of SLE during pregnancy are routinely reported [37]. Pregnancy, specifically during the last trimester, involves a progressive increase of serum estrogen levels, leading to an enhanced immunologic response that, in pregnancies complicated by SLE, predisposes patients to flares of disease activity.

Pathophysiology of lupus flares during pregnancy involves a diminished number and impaired function of a subset of T lymphocytes otherwise known as Treg cells. Treg cells are a vital component in the induction of self-tolerance and the regulation of the immune response, via inhibition of B lymphocytes, CD4+ and CD8+ lymphocytes and suppression of antibody and cytokine production [37].

Detection of lupus flares during pregnancy may prove to be problematic, considering that clinical findings in SLE flares may resemble physiological changes that occur during normal pregnancy. Lupus malar rash consists of erythematous and edematous plaques with or without fine scaling present on the surface. It is typically localized on the nose and cheeks and must not be confused with melasma, a condition that affects up to 3/4 of pregnancies and is characterized by facial symmetric hyperpigmentation [37]. Postpartum hair loss is a common occurrence in women and may be erroneously identified as alopecia secondary to a lupus flare up. Palmar erythema in pregnancy in the absence of musculoskeletal symptoms such as joint tenderness, swelling or effusion, must be treated as a regular occurrence and is generally caused by vasodilation via estrogen upregulation. Alterations in the levels of progesterone during pregnancy predispose women to dyspnea and it must be distinguished from symptoms suggestive of SLE pleurisy.

Hematologic adaptations occurring in normal pregnancies include mild anemia (secondary to hemodilution), leukocytosis (ranging from 5000 to 12 000/mm³) and mild thrombocytopenia (ranging

from 100000 to 150000/mm³) [37,38]. Lupus flare ups are suspected in the presence of hemolytic anemia or lymphopenia (under 1000/mm³).

In normal pregnancies, higher complement levels were reported [38]. Hypocomplementemia is a complication of lupus flares during pregnancy, with complement components such as CH50, C3, C4 falling below the normal range or decreasing by 25% or more as pregnancy advances. In spite of this, total complement levels may remain at normal levels during SLE flare ups in pregnancy [37,38]. Presence of increasing double-stranded DNA antibody levels (anti-dsDNA), decreasing complement components alongside newly developed proteinuria and hypertension are highly specific for lupus nephritis [37]. Renal injury in pregnancy is further suspected when serum creatinine levels of more than 0,8 mg/dl and blood urea nitrogen level over 13 mg/ml are detected [37]. Lupus flares during pregnancy may also present as a doubling of the baseline urine protein amount [37].

DISCUSSION

Differentiating PE from lupus flares during pregnancy can conceivably prove to be a conundrum, since both conditions include the presence of high blood pressure, renal injury, proteinuria and thrombocytopenia, as well as similar signs and symptoms. It is also plausible that PE complicates SLE during pregnancy, in which case timely diagnosis of superimposed PE can be achieved by using the diagnostic criteria developed by the American College of Obstetricians and Gynecologists and include sudden increase in blood pressure and proteinuria, presence of newly developed proteinuria in pregnancy or HELLP syndrome [37].

Onset of hypertension after 20 weeks of gestation, increasing serum values of liver enzymes, inactive urinary sediment, serum acid of over 5.5 mg/ml, stable or negative titres of anti-dsDNA antibodies, normal complement levels with stable components, and levels of urine calcium under 195 mg/24h are indicative of PE. In contrast, onset of hypertension after 20 weeks of gestation, active urinary sediment, rising titres of anti-dsDNA and ANA antibodies, decreasing complement levels and urine calcium over 195 mg/24 h are attributed to active lupus nephritis during pregnancy [37,38]. In some cases, renal biopsy may be required in order to identify active lupus glomerulonephritis.

Novel biomarkers such as PIGF, sFlt-1, PP13, sENG, etc., provide further aid in the differentiation of PE from lupus flares during pregnancy [39]. Suspected PE is successfully ruled out if the sFlt-1 to PIGF ratio, best evaluated under 34 weeks of gestation, is under 38, as indicated by the “PROGNOSIS” study [38]. Patients with active SLE during pregnancy present with normal values of sFlt-1 to PIGF ratio and mUta-PI.

Women with superimposed PE on chronic glomerulonephritis have reported significantly elevated levels of sFlt-1 and markedly decreased levels of circulating PIGF compared to pregnant patients with severe PE [39]. Increased serum triglycerides [38], sFlt-1 and kynurenic acid levels, decreased PIGF levels, presence of ADMA, NO, VEGF and high HbA1c levels provide further aid in the early prediction of risk of PE development [23].

CONCLUSION

Preeclampsia can complicate active lupus during pregnancy, however it is important to accurately and promptly differentiate PE from superimposed PE on active lupus glomerulonephritis, since management of SLE during pregnancy is distinct from that of women presenting with PE in absence of lupus disease. Active lupus nephritis at the moment of conception reported poor obstetric results and elevated risk for lupus flares during pregnancy. Treatment options for lupus flares in pregnancy typically include hydroxychloroquine, prednisone administered in low doses or intravenous pulse therapy with methylprednisolone and azathioprine.

Women with known SLE should consult with their obstetrician and rheumatologist in order to accurately pinpoint the optimal moment for conception. Patients are advised to postpone conception until clinical remission of SLE for at least six months has been proven. Furthermore, certain medication used for lupus treatment may have teratogenic effects and the treatment regimen must be adjusted accordingly.

Although biomarkers such as sFlt-1 and PIGF are currently used for prediction of suspected preterm PE, further research must be done in order to identify novel biomarkers that predict term disease and that improve differential diagnosis of PE and lupus flare in pregnancy.

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