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Biochemical Markers as Diagnostic Markers of Gestational Pyelonephritis

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Abstract Gestational pyelonephritis is a specific inflammatory process of the kidneys of pregnant women. The disease is characterized by the appearance not only in the gestational but also in the postpartum period. The frequency of the disease depends on many factors - environmental, alimentary, geographical, etc. The disease is accompanied by the possible presence of gestational and perinatal complications such as preeclampsia, fetoplacental insufficiency, premature birth, fetal anomalies. This article presents modern literary data on gestational pyelonephritis.

Keywords Gestational pyelonephritis, Kidneys, Nephron

1. Introduction

Pyelonephritis during pregnancy can cause serious complications in pregnant women. It is the most common non-obstetric indication for antenatal hospitalization, and its associated risk factors, diagnosis, and treatment during the antenatal period are well described [1–4]. Serious complications associated with pyelonephritis during pregnancy are common. Sepsis and septic shock occur secondary to pyelonephritis more often than secondary to any other infectious process during pregnancy [5]. Acute respiratory distress syndrome complicates approximately 1–8.5% of cases of pyelonephritis [6,7]. Intensive care unit (ICU) admission is often necessary.

Pyelonephritis is a common complication of pregnancy, affecting 1–2% of pregnancies, and a frequent reason for antenatal hospitalization [1,2]. Pyelonephritis during pregnancy generally has a good prognosis [1,2]; however, it can be associated with severe maternal morbidity, such as Gram-negative sepsis [3-6], renal failure [7], and acute respiratory distress syndrome [8-12].

Infection can induce systemic inflammatory response syndrome (SIRS) and activation of the coagulation cascade [1-6], leading to multiorgan damage and failure. During systemic inflammation, activated monocytes express tissue factor on their membrane [11], and higher tissue factor concentrations in plasma [12] and bronchoalveolar lavage [2] have been linked to the pathophysiology of acute lung injury complicating sepsis. Thrombin generation leads to increased inflammatory processes [4], which are at least in part mediated by the thrombin receptor, also known as the protease-activated receptor (PAR). This receptor can also be activated by a complex of tissue factor, activated factor VII (FVIIa), and activated factor X (FXa) [5]. Activation of PAR receptors leads to the synthesis and secretion of inflammatory mediators (e.g., interleukin (IL)-6 and IL-8) by monocytes and endothelial cells [5].

Originally described in 1977 as a circulating protein in bovine plasma, ZPI is a member of the serpin proteinase inhibitor superfamily. Importantly, ZPI can inhibit other coagulation factors, such as XIa, in the absence of protein Z.

The liver is thought to be the primary source of protein Z, like other vitamin K-dependent factors, and lower plasma concentrations of this protein are observed in patients with liver disease and neonates. However, other sources are possible. We have demonstrated immunoreactivity to protein Z in human placenta (Romero, Broze, Kim, unpublished observations). Patients taking oral contraceptives have higher plasma protein Z concentrations [2]. There is controversy regarding changes in plasma protein Z concentrations between pregnant and non-pregnant women [12]. Plasma protein Z concentrations vary widely in normal individuals, and this appears to be under genetic control. The same applies to ZPI [10]. The exact functions of protein Z and ZPI remain controversial. However, accumulating evidence suggests that this complex inhibits, slows, and reduces thrombin generation through inhibition of factor X activity. Protein Z deficiency has been associated with a moderate risk of thrombosis [18], and this risk is increased when protein Z deficiency is associated with a thrombophilic state. Interestingly, some researchers have suggested that protein Z deficiency may predispose to bleeding. However, these observations have not been replicated [17].

Protein Z deficiency has been associated with adverse pregnancy outcomes: a higher proportion of patients with a previous fetal death (10–15 weeks of gestation) had protein

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Z deficiency (<1 mg/L) compared with controls [11], and (2) patients with adverse pregnancy outcomes (including preeclampsia, IUGR, recurrent unexplained vaginal bleeding, and preterm labor) had significantly lower mean plasma protein Z concentrations than patients with a normal pregnancy outcome. The authors suggested that changes in maternal plasma protein Z concentrations may play an important role in regulating thrombin generation during pregnancy. This is relevant since excessive thrombin generation is associated with preterm birth with intact or ruptured membranes [18], preeclampsia, and SGA fetuses. In contrast, a recent study [16] demonstrated that the median plasma protein Z concentration in patients with preeclampsia, IUGR, and late fetal death (IUFD) was not significantly different from that in patients with normal pregnancies. However, the authors reported a higher incidence of protein Z deficiency (<1.2 mg/L) among patients with IUFD and IUGR compared to patients with normal pregnancies [12].

Pregnant women with gestational pyelonephritis are known to exhibit phenotypic and metabolic changes in granulocytes and monocytes that are consistent with exaggerated systemic intravascular inflammation in the mother [10]. Systemic inflammation is associated with activation of the hemostatic system [14], particularly in patients with sepsis [11]. Three mechanisms have been proposed to explain this, which are detailed below.

Proinflammatory cytokines, such as IL-1β and tumor necrosis factor-α, increase tissue factor mRNA and protein expression by monocytes [18] and macrophages [10]. Increased tissue factor bioavailability can lead to the formation of a tissue factor/FVIIa/FXa complex, which in turn generates thrombin and activates the protease-activated receptor PAR-2. The latter enhances IL-6 production [16]. Thus, a reinforcement loop exists between inflammation and the coagulation system. For a more detailed description of the close interrelationship and importance of the relationship between inflammation and coagulation, the reader is referred to recent reviews on this topic [14]. This interaction is particularly important in obstetrics, as placentas often have a mixture of thrombotic and inflammatory [4]. Evidence in support of this concept includes the observation that administration of antibodies against the FXa binding site of tissue factor/FVIIa complexes attenuates tissue injury and thrombosis in baboons with E. coli sepsis [9]. The proposed mechanism of action is that the tissue factor/FVIIa complex cannot activate PAR-2 without the involvement of factor Xa [9]. Thus, during systemic inflammation, FXa plays a dual role: activation of the prothrombinase complex, leading to thrombin generation, and amplification of the inflammatory process by inducing IL-6 secretion by endothelial cells and monocytes [15]. As shown in a previous study, factor Xa inhibition reduces the inflammatory and thrombotic complications of systemic inflammation during sepsis. Intensive care unit (ICU) patients who developed acute respiratory distress syndrome (ARD) had higher plasma concentrations of tissue factor, but not tissue factor pathway inhibitor, compared to ICU patients who did not develop ARD [12]. This observation suggests that lung injury observed during systemic inflammation may result from a failure to maintain an adequate balance between activated coagulation cascade proteases (i.e., tissue factor, FXa) and their natural inhibitors (i.e., tissue factor pathway inhibitor). One possibility is that the low plasma maternal protein Z concentrations observed in patients with pyelonephritis are due to increased protein Z consumption resulting from increased FX activation during systemic inflammation [8].

Normal pregnancy is characterized by complement activation [9], and we hypothesized that this phenomenon may be a compensatory mechanism aimed at protecting the host from infection [9]. Pregnant patients with pyelonephritis have significantly higher concentrations of complement, C5a, than those without pyelonephritis [10]. C5a causes a 4.9-fold increase in tissue factor activity and a 3.75-fold increase in tissue factor mRNA expression by endothelial cells [10]. Moreover, C5a administration to animals increases the procoagulant activity of alveolar macrophages by 5-6-fold through tissue factor activation [10]. Taken together, these observations suggest that complement activation in pyelonephritis promotes activation of the coagulation cascade.

During severe systemic inflammation, physiological anticoagulant pathways are suppressed [9]. Plasma antithrombin III concentrations are markedly reduced, and protein C activity is impaired [17], leading to decreased anticoagulant activity, further exacerbating the hypercoagulable state observed during systemic inflammation.

A novel lower median protein Z concentration was observed in patients with pyelonephritis during pregnancy. One explanation for this finding is that the prothrombotic state of normal pregnancy [8-11], associated with increased factor Xa production, is exacerbated during acute infection/ inflammation. The protein Z-ZPI complex is involved in counteracting the effects of excess factor Xa and may be consumed in this context. Importantly, in vitro experiments reported consumption of ZPI, but not protein Z [14]. However, because protein Z circulates bound to ZPI, immunoreactive protein Z determinations reflect not only protein Z but also the concentration of protein Z/ZPI complexes [17]. Thus, the lower median plasma protein Z concentration may reflect decreased circulating concentrations of this complex. The extent to which this phenomenon occurs in the non-pregnant state requires further study.

In conclusion, patients with pyelonephritis during pregnancy have lower median maternal plasma protein Z concentrations than healthy pregnant women.

Despite favorable outcomes in most patients, pregnant women with pyelonephritis are at risk of developing preterm labor, adult respiratory distress syndromes, sepsis, and even death [19]. Indeed, acute pyelonephritis (AP) is the most common cause of septic shock during pregnancy [7–9]. Sepsis is defined as a systemic inflammatory response caused by bacteria or bacterial products. During an episode of sepsis, leukocyte activation, increased levels of several pro- and anti-inflammatory cytokines/chemokines/generation of reactive oxygen species, activation of the coagulation/

complement systems, and endothelial dysfunction occur, leading to multiple organ failure. Recently, angiogenic factors have been implicated in the pathophysiology of sepsis [10–16]. In experimental models of sepsis (endotoxemia and/or cecal puncture) [12–14] and observational studies in patients with sepsis [10,11,15,16], increased plasma concentrations of vascular endothelial growth factors (VEGF) [10–12,15], placental growth factors (PlGF) [4], and soluble VEGF receptor (sVEGFR)-1 [13,16] have been observed. Changes in sVEGFR-1 are considered an adaptive response to infection and have survival implications [13,14], as administration of adenovirus expressing sVEGFR-1 [12] or exogenous sVEGFR-1 [13] attenuates the inflammatory response and reduces morbidity/mortality in mice [12,13]. It is unknown whether these changes in angiogenic factors in response to infection are also present in pregnant women. Most studies of angiogenic factors during pregnancy have focused on preeclampsia (PE), a pregnancy-specific disorder that has pathophysiological changes that overlap with those of sepsis. PE is characterized by new-onset hypertension and proteinuria in the second half of pregnancy. Endothelial dysfunction was initially thought to be a central feature of the pathophysiology of PE [17]. However, Redman et al. proposed that maternal preeclampsia syndrome is due to an exaggerated maternal intravascular inflammatory response to pregnancy [18]. Endothelial dysfunction in preeclampsia is part of a generalized intravascular inflammatory response involving circulating leukocytes and the coagulation and complement systems. Although the primary insult responsible for these abnormalities remains unclear [15], it has been postulated that poor placentation and reduced blood flow (or ischemia-reperfusion injury) to the intervillous space of the placenta early in pregnancy lead to the release of factors into the maternal circulation that cause systemic endothelial cell dysfunction [17], intravascular inflammation [5,6], and multiple organ damage. Candidates for these unknown factors include oxidative stress metabolites [3], syncytiotrophoblast microparticles, cytokines [2], angiotensin II receptor antibodies, and sVEGFR-1, a potent natural antiangiogenic factor VEGF [7].

An imbalance between angiogenic (VEGF and PlGF) and antiangiogenic factors (sVEGFR-1 and soluble endoglin (sEng)) has been implicated in the pathophysiology of PE. PlGF is a major member of the VEGF family that can bind to VEGFR-1 and enhance the VEGF angiogenic response on endothelial cells, particularly under pathological conditions such as limb ischemia or wound healing [14]. Soluble VEGFR-1 exerts its antiangiogenic activity by binding to VEGF or PlGF and preventing VEGF binding to its functional ligand VEGFR-2 on endothelial cells [2,4]. sEng modulates the action of transforming growth factor (TGF)-β1 as well as TGF-β3 [14]. Indeed, patients with LE exhibit an angiogenic factor profile consistent with an "antiangiogenic state," characterized by elevated plasma concentrations of sVEGFR-1 and sEng; but decreased plasma concentrations of unbound VEGF and PlGF [3]. These changes have been observed before clinical disease manifestation [6,8,11]. The role of sVEGFR-2 in human disease is unclear, and this protein has received less attention due to its lower affinity for VEGF binding than sVEGFR-1 [15]. However, plasma sVEGFR-2 concentrations may be a surrogate marker of endothelial cell function in the maternal circulation, as VEGF signaling through the membrane isoform of this protein is required for endothelial cell function and survival [6]. Similarly, decreased plasma sVEGFR-2 concentrations in preeclampsia have been observed before clinical diagnosis of this syndrome [7]. Although the balance between angiogenic and antiangiogenic factors is necessary for fetal and placental development, changes in these factors during pregnancy in the context of infection have not been studied. The aims of this study were (1) to investigate whether maternal plasma PlGF, sEng, and sVEGFR-2 concentrations are altered in pregnancies complicated by AP; and (2) to determine whether these changes differ from those observed in PE [17].

2. Conclusions

An analysis of current Russian and international literature has shown that the etiology and pathogenesis of gestational pyelonephritis are highly multifactorial. Anatomical, biochemical, and pathophysiological factors contribute to the development of the inflammatory process. Immunological factors and endothelial dysfunction also play significant roles in the disease. The potential for early diagnosis, complication prevention, and timely treatment of pregnant women with gestational pyelonephritis is supported by the use of classic minimally invasive diagnostic methods (ultrasound, Doppler ultrasound, and MRI) and treatment (stenting, puncture nephrostomy).

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