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Uric Acid as a Pathogenic Factor in Preeclampsia

Shannon A. Bainbridge, PhD[1,2] and **James M. Roberts, MD**[1,2,3]

[1]Magee-Womens Research Institute, University of Pittsburgh, Pittsburgh, PA, USA

[2]Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh, Pittsburgh, PA, USA

[3]Department of Epdiemiology, University of Pittsburgh, Pittsburgh, PA, USA

Abstract

Hyperuricemia is a common finding in preeclamptic pregnancies evident from early pregnancy. Despite the fact that elevated uric acid often pre-dates the onset of clinical manifestations of preeclampsia, hyperuricemia is usually considered secondary to altered kidney function. Increased serum uric acid is associated with hypertension, renal disease and adverse cardiovascular events in the non-pregnant population and with adverse fetal outcomes in hypertensive pregnancies. We hypothesize that an elevated concentration of uric acid in preeclamptic women is not simply a marker of disease severity but rather contributes directly to the pathogenesis of the disorder. Using epidemiological and experimental evidence, gained largely outside of pregnancy, we will propose pathogenic roles for uric acid in preeclamptic pregnancies. Uric acid's ability to promote inflammation, oxidative stress and endothelial dysfunction will be highlighted with discussions of the potential impact on placental development and function and maternal vascular health.

1. Introduction

Hyperuricemia is a common finding in preeclamptic pregnancies. The elevation of uric acid in preeclamptic women often precedes hypertension and proteinuria [1], the clinical manifestations used to diagnose the disorder. There are several potential origins for uric acid in preeclampsia; abnormal renal function, increased tissue breakdown, acidosis and increased activity of the enzyme xanthine oxidase/dehydrogenase [2]. However, despite hyperuricemia antedating other clinical findings of preeclampsia, it has historically been ascribed to impaired renal function. Outside of pregnancy, hyperuricemia is considered a risk factor for hypertension, cardiovascular and renal disease [2]. This evidence, as well as the observation that severity of preeclampsia increases with increasing uric acid, questions whether uric acid may play a role in the pathophysiology of preeclampsia. While this concept is largely unstudied, we expand upon ideas forwarded by Kang [3] to share in the hypothesis that an elevated concentration of uric acid in preeclamptic women is not simply a marker of disease severity but rather contributes directly to the pathogenesis of the disorder. We hypothesize that uric acid acts adversely upon both the placenta and maternal vasculature. In this presentation we will discuss the potential effects of uric acid on placental development and placental function. Further, we will examine the potential negative impact

Corresponding Author: Shannon Bainbridge, Lab 620, Magee-Womens Research Institute, 204 Craft Ave, Pittsburgh, PA, USA, 15213, Shannon.bainbridge@gmail.com, (412) 641-3717.

of uric acid on the maternal cardiovascular system with specific emphasis on its effects upon endothelial function and repair, inflammation and vascular tone.

1.1. Uric Acid

Uric acid is a product of purine degradation catalyzed by the enzyme xanthine dehydrogenase/xanthine oxidase (XDH/XO). XDH is converted to its oxidase form XO by several stimuli including ischemia [4]. Purine metabolism by XO couples the production of uric acid with the production of the free radical superoxide (O_2^-), and is implicated as a contributor to oxidative stress [4]. XDH/XO is found in most tissues but is concentrated in the liver and gut. Recently, a circulating population of XO has been identified that increases dramatically following ischemic tissue damage [5]. Increased circulating uric acid accompanies similar insults [6]. It is speculated that circulating XO can bind to endothelium and lead to local oxidative injury [7].

Most mammals posses the enzyme uricase, that breaks down uric acid into allantoin, a nontoxic product excreted by the kidney. Humans and great apes, however, do not posses uricase and uric acid clearance is reliant largely upon renal excretion [8]. Uric acid is minimally soluble and its concentration is maintained relatively low in healthy individuals (<6.0 mg/dL). However even low concentrations of uric acid possess biological function. Uric acid is a plasma antioxidant capable of scavenging superoxide, hydroxyl radical and singlet oxygen [9]. It also reduces nitrosylation of tyrosine residues on proteins by peroxynitrite and is capable of maintaining superoxide dismutase activity [10], shown to have beneficial effects in some settings. Conversely, uric acid itself can become a pro-oxidant (urate radical) in a setting of compromised antioxidant availability, particularly reduced ascorbate availability [11]. Uric acid is also a mediator of inflammation stimulating the production of monocyte chemoattractant protein-1, IL-1β, IL-6 and TNF-α [2,12].

1.2. Uric Acid during Pregnancy

Uric acid concentrations are influenced by diet (i.e. high protein, and fructose), alcohol consumption, increased cell turnover, enzymatic defects in purine metabolism or altered kidney function [2]. Estrogen is uricosuric and uric acid concentrations are higher in men and post-menopausal women [13]. In pregnancy uric acid concentrations initially fall 25-35% due to the effects of estrogen, expanded blood volume and increased glomerular filtration rate [14]. However, concentrations slowly rise to those observed in non-pregnant women by term gestation (4-6 mg/dL) [1].

1.3. Hyperuricemia and Preeclampsia

Elevated uric acid concentrations were first noted in preeclamptic women in the late 1800s. Since that time numerous reports have demonstrated a relationship between uric acid concentrations and severity of disease [15,16]. Nonetheless, the clinical utility of hyperuricemia in the management of preeclampsia is controversial. Recently we examined the relationship of high uric acid elevations in pregnant hypertensive women to the endpoints of preterm birth (largely indicated preterm birth for the management of preeclampsia) and growth restriction [16]. Hyperuricemia was present in 16% of women with gestational hypertension without proteinuria and 75% of women with clinically diagnosed PE. Pregnancy hypertension with hyperuricemia was associated with an excess of these adverse fetal outcomes. The increased frequency of preterm birth and growth restriction was present in hypertensive women with elevated concentration of uric acid even in the absence of proteinuria.

In women who go on to develop preeclampsia [16], uric acid concentration is elevated as early as 10 weeks of gestation, a time much earlier than the clinical presentation of the

disorder. Increased uric acid often precedes clinical manifestations of the disease, including reduced glomerular filtration rate [16]. Nonetheless, hyperuricemia has historically been attributed to reduced renal clearance. Uric acid is filtered, reabsorbed and secreted by the kidney. Hypovolemia, an early change in preeclampsia, increases uric acid reabsorption which could increase serum uric acid concentrations. However, increased uric acid precedes the reduction in plasma volume [17]. Increased uric acid production from maternal, fetal or placental tissues through heightened tissues breakdown (ie. increased substrate availability) and/or increased XO activity could also explain the increased concentration. The specific stimuli responsible for increased XO activity in preeclamptic women are unclear. The possible roles of placental ischemia-reperfusion injury, reduced antioxidant capacity and oxidative stress will be discussed below.

1.4. Uric Acid as a Pathogenic Vascular Factor

Evidence for a pathogenic role of uric acid is increasing. In the non-pregnant population hyperuricemia is an independent predictor of cardiovascular and renal disease in both the general population and in subjects with chronic hypertension [2]. Uric acid is also a marker for adverse cardiovascular events in patients with established cardiovascular disease [2].

Experimental studies also support a pathogenic role for uric acid. Rats rendered experimentally hyperuricemic through administration of oxonic acid, an uricase inhibitor, develop crystal-independent renal injury and vascular disease in addition to glomerular and systemic hypertension. Inhibiting elevations in uric acid pharmacologically with allopurinol, a xanthine oxidase inhibitor, prevented these changes [18].

2. Potential Effects of Uric Acid on Placental Vascular Development, Structure and Function

2.1. Uric Acid and Placental Development

The placental trophoblast modifies its phenotype over the course of gestation, switching from a highly proliferate to a highly invasive cell subtype. This allows for adequate placental development and invasion of maternal decidua and spiral arterioles. To date we can find no studies examining the effects of uric acid on trophoblast cells. Our discussion of the impact of uric acid on placental growth and development is speculative and based upon phenotypical and functional similarities between endothelial cells and trophoblast cells [19]. Uric acid has a profound effect on both endothelial cell proliferation and migration, inhibiting serum-induced proliferation in HUVEC cells by 50% and inhibiting HUVEC migration by as much as 75% [20]. These effects are a direct result of uric acid uptake by endothelial cells as treatment with probenecid, an inhibitor of organic anion transport, attenuated these effects [20].

Invasive extra villous cytotrophoblast cells invade maternal spiral arterioles with associated vascular remodeling. This results in large diameter, flaccid vessels with no responsive smooth muscle in the vessel wall. In preeclampsia this tightly regulated re-modeling process does not take place adequately, resulting in compromised oxygen and nutrient delivery to the placenta. Nitric oxide (NO) production facilitates trophoblast migration and invasion both in-vitro and in animal models [21,22]. Moreover, eNOS is present in invading cytotrophoblast cells [23]. Uric acid reduces NO production in endothelial cells [20] and a similar effect in trophoblast could modify the migratory and invasive phenotype of trophoblast cells. Since uric acid is increased in women destined to develop preeclampsia prior to 10 weeks gestation it is plausible that uric acid could contribute to inadequate trophoblast invasion and spiral arteriole remodeling. Furthermore, localized increased uric

acid production is also possible as elevations in XO enzyme and activity have been observed in invasive cytotrophoblast cells of preeclamptic women [24].

2.2. Uric Acid and Placental Vascular Structure and Function

Normal placental vascular structure and transport function are ultimately responsible for transporting required oxygen and nutrients to the developing fetus. Uric acid is capable of damaging adult vasculature [2] and could have similar effects in the placentae of preeclamptic women. Uric acid enters smooth muscle cells through organic anion transporters and activates intracellular mitogen-activated protein kinases (i.e. p38) and nuclear transcription factors (i.e NFk-B) [12]. In vitro uric acid stimulates the production of: platelet derived growth factor [25], the vasoconstrictors thromboxane and angiotensin II [26,27], and markers of inflammation such as C-reactive protein [20]. Thus, uric acid treatment of smooth muscle cells results in a proliferative and pro-inflammatory phenotype. Interestingly some of these effects of uric acid on smooth muscle cells are attenuated in the presence of antioxidants [12] suggesting a pathogenic role for the urate radical.

The placental vasculature lacks autonomic innervation [28], relying entirely upon locally produced or circulating substances for hemodynamic control. The primary vasoactive compound responsible for the maintenance of optimized placental perfusion is endothelial derived NO. In hyperuricemic rats uric acid decreases eNOS activity limiting NO availability [20] and up-regulates COX-2 expression with increased generation of the potent vasoconstrictor thromboxane [26]. A similar vasoconstrictive effect of uric acid in the placentae of women with preeclampsia would compromise placental perfusion, and could inhibit fetal growth.

2.3. Uric Acid and Placental Redox Balance

Increased placental oxidative stress is a well-documented feature of preeclampsia. Oxidative imbalance results from increased pro-oxidant generation coupled with insufficient antioxidant capacity. Under normal circumstances uric acid scavenges oxidizing agents known to play a role in the placental pathologies of preeclampsia [9]. This anti-oxidant function of uric acid results in the transformation of uric acid into a free radical, a urate radical [29]. Under normal circumstances, urate is quickly recycled back to its anti-oxidant state through the actions of ascorbate [11]. In a setting of reduced ascorbate availability, as is present in preeclamptic women [30], the urate radical persists and can potentially oxidatively modify placental proteins and lipids.

3. Potential Effects of Uric Acid on Maternal Vasculature

3.1. Uric Acid and Maternal Hypertension

The potential pathogenic effects of uric acid upon the placental vascular bed are also relevant to the maternal vasculature. Preeclamptic women have elevated concentrations of circulating vasopressors, such as thromboxane and endothelin, with parallel decreases in vasodilators such as prostacyclin [31,32]. The maternal vasculature of preeclamptic women also exhibits increased sensitivity to pressor agents [33]. It is proposed that this is in part due to reduced availability of nitric oxide secondary to the endothelial dysfunction [34]. As stated above, elevated uric acid concentration could participate in reduced production of NO and may in part explain the altered endothelial contribution to vascular tone in preeclamptic women. Decreasing uric acid with allopurinol improved endothelial dependant vasodilation in diabetic and congestive heart failure patients [35,36]. Reducing uric acid concentration might be a potential therapeutic strategy for preeclamptic women as well.

3.2. Uric Acid and Inflammation

The preeclamptic environment of heightened inflammation results in endothelial dysfunction and vascular lesions. Uric acid is a potent mediator of inflammation. In vascular smooth muscle cells uric acid increases the concentration of the chemokine monocyte chemoattractant protein-1 (MCP-1) mRNA and protein in a time and dose dependant fashion [12]. Uric acid also stimulates human monocytes to produce the pro-inflammatory cytokines IL-1β IL-6 and TNF-α, [2,12] which are also elevated in the circulation of experimentally induced hyperuricemic animals [37] as well as preeclamptic women [38]. In preeclamptic women the increased concentration of circulating TNF-α was positively correlated to circulating uric acid concentrations [39].

3.3. Uric Acid and Endothelial Repair

Dramatic elevations in circulating uric acid follow an acute ischemia-reperfusion event [40]. This acute rise in uric acid concentrations in animal models induces endothelial progenitor cell (EPC) mobilization [40]. Uric acid is posited to act as a signal for endothelial damage promoting repair of damaged vessels through EPC mobilization. However, this protective role of uric acid is only present with acute increases of circulating uric acid. Increased mobilization of EPCs is not observed in rats rendered chronically hyperuricemic following an induced renal ischemic-reperfusion injury [40]. Thus chronically increased uric acid is associated with blunted release of EPC's. It is of note that these progenitor cells are reduced in preeclampsia [41]. This may be the result of increased usage of these cells in damaged vascular beds or, based on the data outlined above, decreased mobilization of the cells.

3.4. Uric Acid and Maternal Renal Dysfunction

Renal dysfunction is a consistent finding in preeclamptic women. Renal anatomic changes include juxtaglomerular hyperplasia, macula densa atrophy, afferent arterolopathy, glomerular hypertrophy and glomeruloendotheliosis [3]. The mildly hyperuricemic rat model demonstrates remarkably similar renal changes [27,3] including afferent arteriolopathy, mild tubulointerstitial fibrosis, glomerular hypertrophy and eventually glomerulosclerosis with subsequent albuminuria and proteinuria [18]. These uric acid induced pathologies are independent of uric acid crystal formation and can be inhibited by lowering uric acid concentrations. Interestingly, over 20 years ago Nochy reported that the renal lesions observed in preeclamptic women are seen only in hyperuricemic preeclamptics [42].

4. Feed-Forward Cycle of Uric Acid Production in Preeclampsia

How is the hyperuricemia of preeclampsia initiated? The increase in uric acid antedates the reduction of glomerular filtration and hypovolemia [17,1]. Thus it seems unlikely that these two features of preeclampsia, that potently reduce uric acid excretion, are initially responsible. It is possible that women destined to develop preeclampsia come into pregnancy with elevated uric acid as part of the metabolic syndrome or that uric acid production is increased in early pregnancy. There are several plausible sources for increased uric acid in women with preeclampsia, including the fetus, placenta, and maternal organs and vasculature.

Uric acid could contribute to failed placental bed vascular remodeling by impeding trophoblast invasion with resultant reduced placental perfusion, setting the stage for ischemia reperfusion injury to the placenta and oxidative stress. Maternal tissues may also experience ischemic injury due to vasospasm secondary to endothelial dysfunction (also plausibly related to increased uric acid). Ischemic injury and oxidative stress promotes a feed-forward cycle of uric acid production. With tissue injury, purines are liberated and with

hypoxia ATP is degraded to both adenine and xanthine (substrate). Additionally hypoxia is a potent inducer of the holoenzyme xanthine oxidase/dehydrogenase and preferentially increases the oxidase form of the enzyme [4]. With the parallel increases in both substrate and enzyme concentrations, uric acid production will increase. Furthermore vasospasm and loss of fluid secondary to endothelial dysfunction also stimulate renal reabsorption of uric acid [43]. Thus hyperuricemia leads to more uric acid production and less uric acid excretion in a feed forward loop (Figure 1).

5. Summary Speculation

Hyperuricemia is one of the earliest and most consistent observations noted in preeclamptic pregnancies. While elevated concentrations of circulating uric acid are not uniformly seen in every woman with preeclampsia, they do appear to identify a subset of preeclamptic women who are at greater risk for maternal and fetal morbidities. Also, hyperuricemia in pregnant women without proteinuria is at least as good a predictor of fetal morbidity as hypertension and proteinuria. We speculate that uric acid may play direct roles in the pathological processes of preeclampsia at both the level of the placenta and maternal vasculature. The evidence used to formulate this hypothesis was drawn heavily from epidemiological and clinical studies of non-pregnant individuals describing positive associations between hyperuricemia and risk of cardiovascular events, in addition to work demonstrating an independent association between elevated uric acid and poor fetal outcome. The hypothesis is further supported by in-vitro culture studies and hyperuricemic animal models demonstrating several pathogenic effects of uric acid, including pro-inflammatory effects, stimulation of smooth muscle cell proliferation, inhibition of endothelial cell proliferation and migration, promotion of endothelial dysfunction and damage. These insults all play pivotal roles in the pathophysiology of preeclampsia. We propose that there is sufficient evidence to support a pathogenic role for uric acid in this disorder that warrants further investigation.

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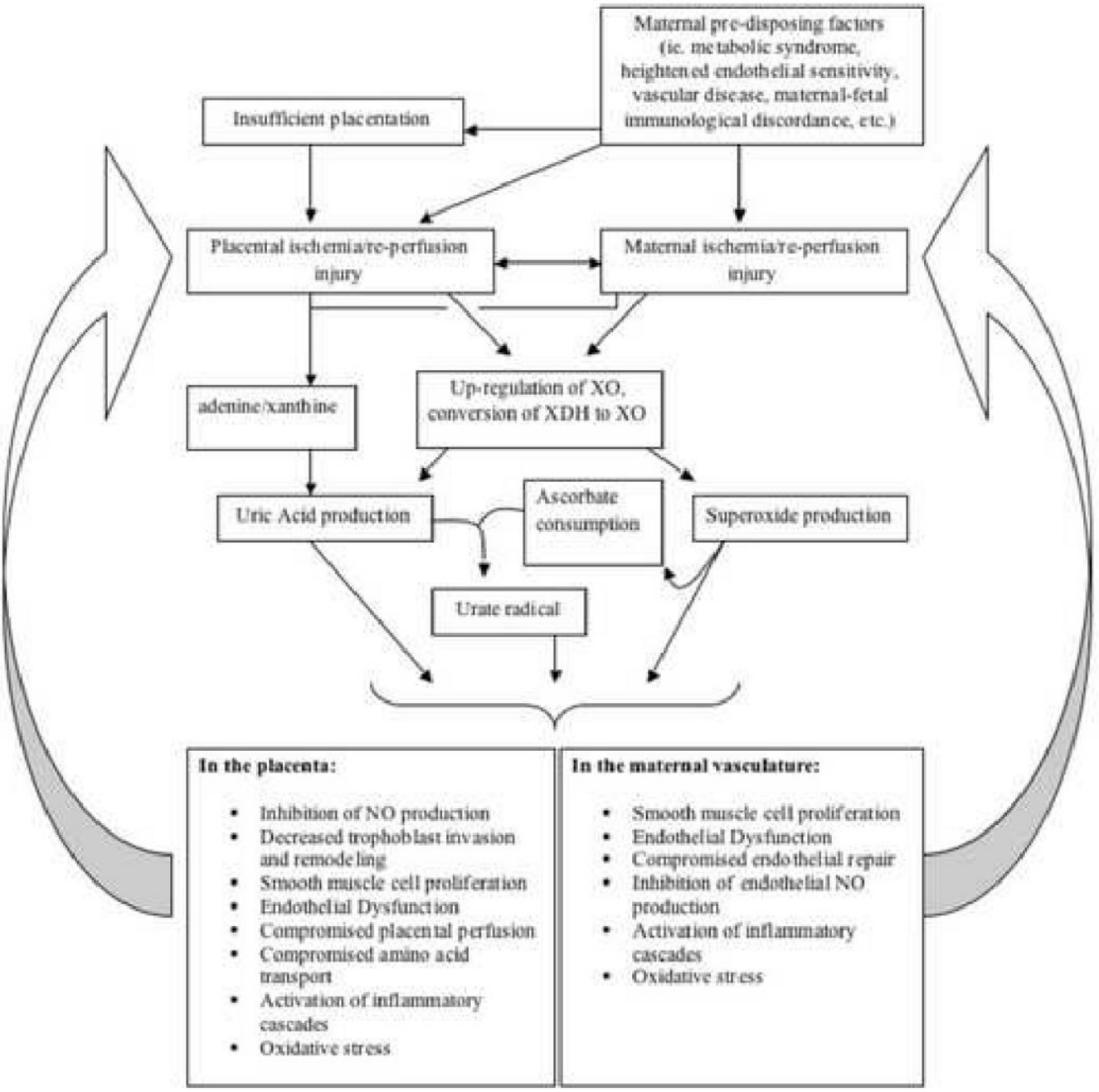

Figure 1.
The feed forward mechanism of uric acid production and potential pathogenic roles of uric acid in the context of preeclampsia.