Uric acid: A hypothetical cause of preeclampsia-eclampsia

We wish to suggest a cause for preeclampsia-eclampsia. This cause has novel features that are of considerable biological interest.

The theory posited by Roberts and his colleagues in 1989 continued to guide research related to preeclampsia-eclampsia aetiology.[1] Drawing on past work that associated preeclampsia with shallow trophoblast invasion and subsequent reduction in placental perfusion, they hypothesized that the ischaemic placenta released a damaging factor(s) into the maternal circulation. Although the identity of this factor was hitherto unknown, the circulating factor was hypothesized to have caused endothelial dysfunction and activation of coagulation cascade, blood pressure abnormalities, and loss of fluid from intravascular space. In our opinion, this placental factor is unsatisfactory for two reasons. First, we believe that the factor that causes endothelial dysfunction is a genetic material of embryonic origin and not a gene product released by the placenta. Without the genetic material, it is not clear why the disease condition will be seen in primigravidas or during the first pregnancy in multiparous women who have changed partner. Second, the placental factor does not cause endothelial dysfunction in subsequent pregnancies if it did not cause damage in the first pregnancy, except when there is multiple gestation or molar pregnancy.

The 1980 discovery of nitric oxide as an endothelial cell-derived relaxing factor resulted in an unprecedented biomedical research of nitric oxide and established it as one of the most important cardiovascular system molecule. A reduction in endothelial cell nitric oxide levels leading to "endothelial dysfunction" was identified by several investigators as a key pathogenic event preceding the development of hypertension. The reduction in endothelial nitric oxide in cardiovascular disease has been attributed to the action of antioxidants that either directly react with nitric oxide or uncouple its substrate enzyme. Gersch and his co-worker demonstrated in 2008 that uric acid reacts directly with nitric oxide in a rapid irreversible reaction, resulting in the formation of 6-aminouracil and depletion of nitric oxide.[2,3]

As a follow-up to these research findings, we designed a study to assess the level of uric acid in maternal circulation during normal pregnancy and found that uric acid level was significantly higher in pregnant women than in none pregnant women with levels in the 4th, 7th, and 8th months being higher when compared to the other months of gestations. Based on this, we proposed that the damaging factor released into the maternatal circulation by the ischaemic placenta is uric acid produced from cells of embryonic origin. This might explain why women with molar and multiple pregnancies develop preeclampsia-eclampsia.

Full details of our study, including the conditions assumed in conducting it, together with the results will be published elsewhere.

Uric acid is generated in the mammalian systems as an end-product of purine metabolism. Hyperuricaemia may result when there is increased synthesis of purine, increased purine intake, increased turnover of nucleic acids, increased tissue breakdown, or increased tissue damage. It possesses free-radical-scavenging properties[4,5] and is the most abundant antioxidant in human plasma.[6,7] In addition, uric acid inhibits system A amino acid uptake[8] and has endogenous danger signalling properties[9] that ultimately lead to suppression of growth rate.

We wish to put forward a radically different evidence for uric acid cause of preeclampsia-eclampsia. This evidence is anthropometric in nature [Figures 1 and 2]. From Figure 1, it can be seen that, during intrauterine life, foetal growth rate is high from week 13 to week 18, but as the foetus enters week 19, the growth rate drops as low as 1 mm/day.[10] We assumed that, during this period, the level of uric acid in maternal circulation is high, reflecting its level in foetal circulation. This high uric acid level in foetal circulation most likely inhibits system A amino acid uptake and triggers endogenous signalling properties of uric acid in foetal tissue, leading to suppression of growth

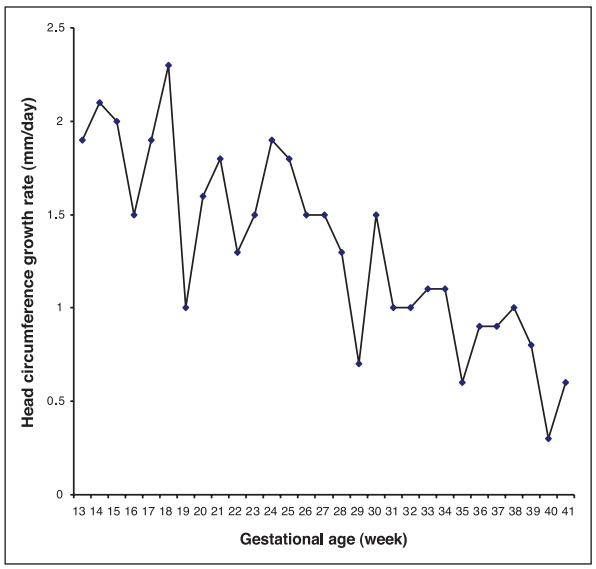

Figure 1: Growth velocity pattern of head circumference in 13,740 Nigerian fetuses in Jos

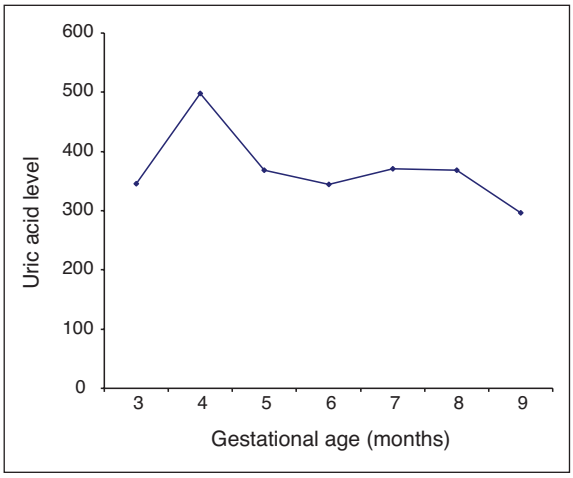

Figure 2: Mean uric acid level in maternal circulation during normal pregnancy

rate in the foetus, as seen during week 19. In addition to suppressing growth rate, it reduces endothelial cell nitric oxide levels, leading to "endothelial dysfunction," which has been described as the key pathogenic event preceding the development of hypertension. Furthermore, suppression of growth rate around the 19th week makes the foetus rapidly loose approximately 318 g. We assumed that, as uric acid level rises in the 4th month of life, it reacts directly with endothelial nitric oxide, thereby depleting it and leading to endothelial dysfunction; hence, the manifestation of preeclampsia-eclampsia as from 20 weeks of gestation. As foetal growth and development continues uric acid level in maternal circulation drops from higher levels at the 4th month only to peak again around the 7th and 8th months of life [Figure 2]. Since the foetal purine that is unique is determined by the fusion of maternal and paternal gametes at fertilization, it elicits immunological response that will protect the endothelial cells of maternal vasculature in subsequent pregnancies. However, when such a woman changes partner, her first pregnancy with the new husband forms different sets of purine at fertilization, which will be new when released in the maternal circulation, thereby eliciting a fresh response in the mother causing endothelial dysfunction. In subsequent pregnancies, the maternal immune system would have developed defences against the uric acid produced.

In multiparous women with twin pregnancies, the level of uric acid produced doubles the level of singleton pregnancies, thereby readjusting the nitric oxide depletion threshold that leads to endothelial dysfunction. Similarly, in molar pregnancy, the level of uric acid produced is much higher than the level in singleton and multiple pregnancies, thereby giving an insight as to why preeclampsia-eclampsia occur earlier in molar pregnancy before 20 weeks.

The novel feature of uric acid as the cause of preeclampsia-eclampsia is the manner in which its synthesis can be regulated using xanthine oxidase inhibitors during the first pregnancy in order to prevent the occurrence of the disease and its ability to activate immune effectors of both the innate and adaptive immune system, thereby preventing the disease in subsequent pregnancies. Towards this end, we are planning to perform randomized clinical trial to determine the usefulness of xanthine oxidase inhibitors in the prevention of preeclampsia-eclampsia as well as its use in the treatment of pre-term labour. It has not escaped our notice that depletion of nitric oxide from the uterine myometrium at term may be responsible for causing the onset of labour.

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REFERENCES

1. Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK. Preeclampsia: An endothelial cell disorder. Am J Obstet Gynecol 1989;161:1200-4.
2. Gersch C, Palii SP, Kim KM, Angerhofer A, Johnson RJ, Henderson GN. Inactivation of nitric oxide by uric acid. Nucleosides Nucleotides Nucleic Acids 2008;27:967-78.
3. Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, Krotoya K, *et al*. Hyperuracaemia induces endothelial dysfunction. Kidney Int 2005;67:1739-42.
4. Kuzkaya N, Weissmann N, Harrison DF, Dikalov S. Interactions of peroxynitrite with uric acid in the presence of ascorbate and thiols: Implications for uncoupling endothelial nitric oxide synthase. Biochem Pharmacol 2005;70:345-54.
5. Robinson KM, Morre JT, Beckman JS. Triuret: A novel product of peroxynitrite-mediated oxidation of urate. Arch Bioch Biophys 2004;423:213-7.
6. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: A hypothesis. Proc Natl Acad Sci USA 1981;78:6853-62.
7. Hediger MA. Kidney function: Gateway to a long life? Nature 2002;417:393-5.
8. Bainbridge SA, von Versen-Hoynck F, Roberts JM. Uric acid

inhibits placental system A amino acid uptake. Placenta 2009;30:195-200.
9. Behrens MD, Wagner WM, Krco CJ, Erskine CL, Kalli KR, Krempski J, *et al*. The endogenous danger signal, crystalline uric acid, signals for enhanced antibody immunity. Blood 2008;111:1472-9.
10. Mador ES, Mutihir JT, Ogunranti JO. Fetal head circumference as an anthropometric index. In: Preedy VR, editor. Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease. UK: Springer; 2012. p.477-516.

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