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Introduction

(Dr Mador)

Every minute a woman dies from pregnancy-related causes and almost 99% of these maternal mortalities occur in developing nations (Nawal, 2008). Despite this shocking death rate, there is little or no research efforts from developing nations geared towards solving this health challenge. In 1987, the international safe motherhood conference convened in Kenya. The conference raised a global awareness of the overwhelming maternal mortality rates in developing nations and formally established the safe motherhood initiative. The goal of the initiative was to reduce maternal mortality by 50% by the year 2000, and announce to the global community the predicament of the pregnant women. Initially, United Nations (UN) agencies and governments focused on 2 strategies to reduce maternal mortality which were increasing antenatal care and training for traditional birth attendants. From all indications, there was no place for research in the strategies employed. By the year 2000, the goal was far from realized. The global community reaffirmed its commitment in 2000, and the United Nations issued 8 Millennium Development Goals (MDGs); the fifth goal (MDG-5) stipulated a reduction of the maternal mortality rate by 75% by 2015. With 2015 around the corner, it is like the outcome will be the same as it was with the safe motherhood initiative in the year 2000.

According to World Health Organization (2005) report, the main causes of maternal deaths are postpartum haemorrhage (24%); indirect causes such as anemia, malaria, and heart disease (20%); infection (15%); unsafe abortion (13%); preeclampsia-eclampsia (12%); obstructed labour (8%); and ectopic pregnancy, embolism, and anesthesia complications (8%). Preeclampsia-eclampsia is a hypertensive, multi-system disease exclusive to human pregnancy whose cause remains unknown (Pennington *et al*., 2012). This disease is characterized by placental hypoxia and/or ischemia, excessive oxidative stress, in association with endothelial dysfunction. It is the most common medical complication of pregnancy

whose incidence has continued to increase worldwide. Risk factors for preeclampsia include nulliparity, multifetal gestations, previous history of preeclampsia, obesity, diabetes mellitus, vascular and connective tissue disorders like systemic lupus erythematosus and antiphospholipid antibodies, age >35 years at first pregnancy, smoking, and African American race (Elosha *et al*., 2012). Among primiparous women, there is a disparity among ethnic groups as the risk in African American women is twice that of Caucasian women, and the risk is also very high in women of Indian and Pakistani origin (Rao *et al*., 2006). Although management of this medical condition is evidence-based, preventive measures/screening tools are lacking and delivery remains the only cure. But why is this disease exclusive to human pregnancy?

Just like any other living organism, man is made from chemical elements which are combined to form molecules such as including fats, carbohydrates, proteins and nucleic acids. These molecules put together make up cells, the basic units of the human body, capable of carrying out life processes which are nutrition, respiration, excretion, growth, movement, irritability and reproduction. An organism either takes in food or if it is a green plant, makes its food from raw materials. The process of taking in or making food and preparing it for use in such activities as respiration and growth is called nutrition. Secondly, an organism is constantly using up energy as it carries out the processes which keep it alive. It obtains the energy it needs by breaking down complex materials into simpler ones. This process is called respiration. Again, an organism increases in size and mass at least while it is young. It also replaces and repairs worn-out or damaged parts of its body throughout life. Once more, an organism is sensitive to changes in the surrounding and responds to them, often by some form of movement. The ability to perceive and respond to stimuli is called irritability. Apart from this, most animals can walk, swim or fly from one place to another. Plants also show movements but most move only parts of themselves while the plant itself remains

fixed to one spot. Movement of the whole organism from one place to another is called locomotion. It is general in animals but rare in plants. Once more, organisms can produce new members of their species through a process called reproduction. Finally, many chemical activities go on in an organism and produce waste products which are substances the organism does not need and which may poison it if they are allowed to build up in the body. Every organism has some means of getting rid of its waste products. The process is called excretion. The common excretory products formed in the bodies of animals are water, carbon dioxide, mineral salts and nitrogenous compounds such as urea, uric acid and ammonia compounds. These products may come either from every cell in the body or from certain parts of the body only. Most of them are products of the body's metabolism, and can be referred to as metabolites. For the purpose of removing waste products from the body, almost all animals are equipped with special excretory organs. The excretory organs in mammals are the kidneys, the lungs, the liver and the skin.

Unlike the majority of mammals, uric acid is the end product of purine metabolism in man, due to the loss of uricase activity during the evolution of hominids. This loss, together with uric acid balance in the kidney and the lifestyle and eating habits of developed countries, has led to a high prevalence of hyperuricaemia and its consequences. Majority of mammals have very low serum urate levels because uric acid is transformed by uricase to allantoin, a very soluble excretion product, which is freely eliminated by the urine (Hayashi *et al*., 2000). The lack of uricase makes uric acid the end product of purine metabolism in humans and other higher primates (Richette *et al*., 2010; Riches *et al*., 2009) and is the main reason why serum uric acid levels in adult males are ~6.0 mg/dl, compared with the majority of mammals who have uric acid levels <0.5–1 mg/dl (Ames *et al*., 1981; Watanabe *et al*., 2002; Johnson *et al*., 2003). This makes human beings particularly susceptible to changes induced by diet (Feig and Johnson,

2009), and hence this is the main reason for humans to be the only mammals who develop gout spontaneously (Doherty, 2009). The origin of uricase is very old, being present in a great variety of organisms, from bacteria to mammals and it has different metabolic activities depending on the host organism. There is a cross-reaction between the uricases of different species, having the same tissue specificity and cell location, as well as similar molecular weight. Hence, it suggests that the uricases of diverse species have a common evolutionary origin (Oda *et al*., 2009). Humans, some higher primates and certain New World monkeys do not show any detectable level of uricase activity. This is due to the appearance of several mutations of its gene during the evolutionary process, which made it non-functional (Wu *et al*., 1992). In other monkeys in the Old and New Worlds, uricase activity is moderate, between two and four times lower than that in mice and rabbits (Oda *et al*., 2009), and also less stable (Wu *et al*., 1992). Wu *et al*. (1992) identified three mutations in the uricase gene in humans, chimpanzees and gorillas, including two nonsense mutations, one of codon 33 and another of codon 187, and a mutation in the splice acceptor signal of exon 3. The codon 33 mutation is also present in the orangutan. Based on the phylogeny of human evolution, Wu *et al.* (1992) established that the codon 33 mutation happened 24 million years ago; the mutation of codon 187 took place 16 million years ago, when the orangutan had already followed another line; and the exon 3 mutation occurred 13 million years ago, affecting the human/gorilla/chimpanzee line ((Wu *et al*., 1992). Later on, Oda *et al*., (2009) did not find any uricase activity in humans, chimpanzees, gorillas, orangutans or gibbons, but they find functional uricase in other monkeys, such as baboons and rhesus monkey. They have found up to eight independent nonsense mutations in hominids without uricase activity. They mainly attribute the loss of uricase activity to the nonsense mutation of codon 33 of exon 2, dating it to 15 million years ago. The promoter region of the gene had probably already been degraded in the evolutionary process by previous mutations, being more likely a gradual loss of uricase activity rather than a single step loss (Oda *et al*., 2009;

Jhonson *et al*., 2005). This is reasonable because the inactivation of the uricase gene in the mouse causes a pronounced hyperuricaemia nephropathy due to urate, resulting in more than half the mutant mice dying before 4 weeks of age (Wu *et al*., 1994). A gradual loss of activity would allow adaptation measures to the new situation to be developed (Jhonson *et al*., 2005). Several independent mutations in the uricase gene occurred during the evolution of hominids as well as in monkeys of the Old and the New Worlds. These mutations have been interpreted as clear evidence of an important evolutionary advantage for the early primates that had increased uric acid (Wu *et al*., 1992; Christen *et al*., 1970). In the same way, as purine degradation is much less complete in higher animals than in others that we consider lower, it is obvious that certain enzymes had been lost during animal evolution and it is assumed that it provided some evolutionary advantage (Hayashi *et al*., 2000). On the other hand, if uric acid was a harmful waste product, it would be difficult to explain how the kidneys recover 90% of filtered uric acid (Kutzing and Firestein, 2008), instead of eliminating it. The evolution of hominids and the physiology of renal urate balance have associated uric acid as something beneficial that we must keep instead of something harmful that has to be removed. These facts have led various authors to propose some hypotheses on the evolutionary advantages of the loss of uricase and the subsequent increase in uric acid.

With this background information one might be led into wondering whether uric acid is not the sole cause of preeclampsia-eclampsia. According to Austin Hill, the causal link between a specific factor (e.g., cigarette smoking) and a disease (such as emphysema or lung cancer) must fulfill certain minimal conditions (Hill, 1965) needed to establish a causal relationship between two items referred to as Hill's criteria of causation. These criteria for causation are:

1. Temporal Relationship: Exposure always precedes the outcome. If factor "A" is believed to cause a disease, then it is clear that factor "A" must

necessarily always precede the occurrence of the disease. This is the only absolutely essential criterion.

2. Strength: This is defined by the size of the association as measured by appropriate statistical tests. The stronger the association, the more likely it is that the relation of "A" to "B" is causal. For example, the more highly correlated hypertension is with a high sodium diet, the stronger is the relation between sodium and hypertension.

3. Dose-Response Relationship: An increasing amount of exposure increases the risk. If a dose-response relationship is present, it is strong evidence for a causal relationship. However, as with *specificity*, the absence of a dose-response relationship does not rule out a causal relationship. A threshold may exist above which a relationship may develop. At the same time, if a specific factor is the cause of a disease, the incidence of the disease should decline when exposure to the factor is reduced or eliminated.

4. Consistency: The association is consistent when results are replicated in studies in different settings using different methods. That is, if a relationship is causal, we would expect to find it consistently in different studies and among different populations. This is why numerous experiments have to be done before meaningful statements can be made about the causal relationship between two or more factors. For example, it required thousands of highly technical studies of the relationship between cigarette smoking and cancer before a definitive conclusion could be made that cigarette smoking increases the risk of (but does not cause) cancer. Similarly, it would require numerous studies of the difference between male and female performance of specific behaviors by a number of different researchers and under a variety of different circumstances before a conclusion could be made regarding whether a gender difference exists in the performance of such behaviors.

5. Plausibility: The association agrees with currently accepted understanding of pathological processes. In other words, there needs to be some theoretical basis for positing an association between a vector and disease, or one social phenomenon and another.

6. Consideration of Alternate Explanations: In judging whether a reported association is causal, it is necessary to determine the extent to which researchers have taken other possible explanations into account and have effectively ruled out such alternate explanations. In other words, it is always necessary to consider multiple hypotheses before making conclusions about the causal relationship between any two items under investigation.

7. Experiment: The condition can be altered (prevented or ameliorated) by an appropriate experimental regimen.

8. Specificity: This is established when a single putative cause produces a specific effect. This is considered by some to be the weakest of all the criteria. The diseases attributed to cigarette smoking, for example, do not meet these criteria. When specificity of an association is found, it provides additional support for a causal relationship. However, absence of specificity in no way negates a causal relationship. Because outcomes (be they the spread of a disease, the incidence of a specific human social behavior or changes in global temperature) are likely to have multiple factors influencing them, it is highly unlikely that we will find a one-to-one cause-effect relationship between two phenomena. Causality is most often multiple. Therefore, it is necessary to examine specific causal relationships within a larger systemic perspective.

9. Coherence: The association should be compatible with existing theory and knowledge. In other words, it is necessary to evaluate claims of causality

> within the context of the current state of knowledge within a given field and in related fields. What do we have to sacrifice about what we currently know in order to accept a particular claim of causality?

The connection between these risk factors and preeclampsia is poorly understood hence the need of further research. The differences in risk among ethnic groups suggest a strong role for genetic factors in the pathogenesis of preeclampsia. Towards this end, whatever is causing this disease condition should fit into the Hill's causative criteria. Most theories on the aetiology of preeclampsia suggest that the disease is a cascade triggered by combination of abnormal maternal inflammatory response, endothelial cell activation/damage with deranged haemodynamic milieu, and deranged immunity. The precise trigger that unifies the deranged vascular, immune and inflammatory response remains to be explained. In this book, emerging concept in pathogenesis of preeclampsia is discussed and therapeutic options reviewed.