3

The Quest

(Dr Mador)

Preeclampsia is the occurrence of hypertension and significant proteinuria in a previously healthy woman on or after the 20th week of gestation and is said to occur in about 2–8% of pregnancies. Literature search shows that the aetiology of this disease has been studied by a large number of investigators in different parts of the world and the search is still going on. According to McMillen (2003), Francois Mauriceau was the first person to scientifically describe eclampsia and to point out that primigravidas were at greater risk for convulsions compared to multigravidas. As for the causes of convulsions, Mauriceau ascribed convulsions to either abnormalities in lochial flow or intrauterine fetal death. After the introduction of the word "eclampsia," Bossier de Sauvages (1739) differentiated eclampsia from epilepsy (Chesley, 1978; Friedlander, 2001). In 1797, Demanet noted a connection between edematous women and eclampsia (Chesley, 1978) while John Lever discovered albumin in the urine of eclamptic women in 1843 (Thomas, 1935). The connection between premonitory symptoms during the later months of pregnancy and the development of puerperal convulsions was also recognized in 1843 by Dr. Robert Johns. These premonitory symptoms included headache, temporary loss of vision, severe pain in the stomach, and edema of the hands, arms, neck, and face (Johns, 1843). With these developments, physicians were now aware that the presence of edema, proteinuria, and headaches should raise concern about the possibility of convulsions (Sinclair & Johnston, 1858). In 1897, Vaquez and Nobecourt were credited with the discovery of eclamptic hypertension (Chesley, 1978). As a result of these contributions, the concept of the preeclamptic state was recognized. Today, preeclampsia is known to be a pregnancy associated disease of primigravidas, occurring mainly after 20weeks gestation. When present in multiparous women, it is commonly associated with multiple pregnancies or in their first pregnancy with a new partner. The occurrence of preeclampsia in molar pregnancy hints that the presence of a fetus is not essential to the development of the disease.

Despite active research for centuries, the aetiology of this disorder exclusive to human pregnancy is a mystery, and that is why it is still a disease of theories. In the 18th century for example, Boissier de Sauvages distinguished eclampsia from epilepsy. Along with the distinction he made in disease classification, de Sauvages offered his views on the cause of convulsions. He believed that convulsions resulted from nature trying to free the organism of any morbid element (Temkin, 1971). Theories on disease causation continued to be proposed and thoroughly discussed in the writings of 19th century physicians. In his work entitled Introduction to the Practice of Midwifery, Dr. Thomas Denman (1821) focused much attention on the labours affected by convulsions. Although Denman credited convulsions to certain traditions and etiquettes associated with living in big cities and towns, he noted that the greatest risk of convulsions came from the uterus. According to Denman, as the uterus expanded with pregnancy, greater pressure was placed upon the descending blood vessels. Such an increase in pressure lead to the regurgitation of blood in the head and resulted in an overload of the cerebral vessels and subsequent convulsions (Denman, 1821).

In his 1849 work titled "Parturition and the Principles and Practice of Obstetrics"; Dr. William Tyler Smith challenged the theory of cerebral congestion, for he believed that pregnancy was a state of increased fullness in circulation. Given that contractions during the second stage of labour normally interfered with the circulation of blood, he believed that more cases of convulsions would be observed if such congestion caused convulsions. In contrast, Smith attributed puerperal convulsions to several other causes which include: any mechanical or emotional stimulus applied in excess to the spinal centre; bloodletting; variations in the wind, temperature, and other atmospheric changes; irritation of the uterus, uterine passages, intestinal canal, and the stomach; and "toxic" elements. As for Smith's theory on "toxic" elements, he believed that preservation of health during pregnancy depended on the exponential increase in the elimination of wastes (e.g.,

secretions of the bowels) and debris from the maternal and fetal systems. Failure to do so resulted in a "toxemia" in which morbid elements accumulated in the blood causing irritation to the nervous center (Smith, 1849).

Although researchers in the 20th century failed to uncover the aetiology of preeclampsia, much progress was made in the understanding of pathophysiological changes associated with its development. In the 1960's, several groups described dramatic differences in placental physiology between placentas from pregnancies affected by preeclampsia versus placentas from pregnancies unaffected by preeclampsia. Through the examination of placental bed biopsies, it was discovered that placental trophoblast cells failed to adequately invade maternal spiral arteries and convert the arteries from small muscular vessels into large, low resistant vessels in preeclampsia. With the lack of spiral artery conversion, arterial lumen diameter and distensibility was limited, resulting in restricted blood flow to the placenta and growing fetus (Brosens *et al*., 1967; Brosens *et al*., 1972; Gerretson *et al*., 1981; Kong *et al*., 1986). Although these findings were instrumental in laying the groundwork for the current understanding of preeclampsia-eclampsia, not all theories or scientific discoveries have readily been accepted by the scientific community. Published in the American Journal of Obstetrics and Gynecology in 1983, the Hydatoxi lualba (parasitic worm) theory of preeclampsia was one such conjecture swiftly refuted by the scientific community. Under this theory, it was posited that the development of preeclampsia-eclampsia may be associated with the presence of a worm-like organism. Specimens collected from women with preeclampsia-eclampsia, including peripheral circulating blood, bloody fluid on the maternal surface of the placenta, and umbilical cord blood, were found to be positive for Hydatoxi lualba (Lueck *et al*., 1983). However, several other research groups demonstrated that starch powder from gloves, cellulose debris from common laboratory paper products, and alterations in staining technique

produced the same characteristic worm-like organisms (Papoutsis *et al*., 1983; Sibai & Spinnato, 1983), which lead to refutation of the theory.

Unlike the parasitic worm theory, the theory posited by Roberts and his colleagues in 1989 continues to guide research related to preeclampsia-eclampsia aetiology. Roberts and his colleagues posited that preeclampsia represented an endothelial disorder. Drawing on past work that associated preeclampsia with shallow trophoblast invasion and subsequent reduction in placental perfusion, they hypothesized that the ischemic placenta released a damaging factor(s) into the maternal circulation. Although factor identity was unknown, the circulating factor was hypothesized to have caused endothelial dysfunction and would lead to activation of the coagulation cascade, blood pressure abnormalities, and loss of fluid from the intravascular space (Roberts *et al*., 1989). In the opinion of Mador *et al*., (2013), this placental factor is unsatisfactory for two reasons. Firstly, they believe that the factor which 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 first pregnancy in multiparous women who have changed partner. Secondly, 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” has been 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. As a follow-up to this research finding, a study was designed (Mador *et al*., 2013) to assess the level of uric acid in maternal circulation during normal pregnancy and it was found out that uric acid level was significantly higher in pregnant women than nonpregnant women with levels in the 4^{th}, 7^{th} and 8^{th} months being higher when compared to the other months of gestations. Based on this, it was proposed that the damaging factor released into the maternal circulation by the ischaemic placenta is uric acid produced from genetic material of cells of embryonic/fetal origin.