Retraction: “Historical perspective of preeclampsia from the viewpoint of pathogenesis: Ancient times to mid-20th century” published in Hypertension Research in Pregnancy, 2014; 2: 40–46, has been retracted at the request of authors because the article replicates significant portions of copyrighted text from an earlier published article, “A Historical Overview of Preeclampsia-Eclampsia,” by Bell, M., published in the *Journal of Obstetric, Gynecologic & Neonatal Nursing* (JOGNN), 39, 510-518; 2010. DOI: 10.1111/j.1552-6909.2010.01172.x (hyperlink DOI to: <http://onlinelibrary.wiley.com/doi/10.1111/j.1552-6909.2010.01172.x/abstract>). The authors regret the error.

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PERSONAL PERSPECTIVE

Historical perspective of preeclampsia from the viewpoint of pathogenesis: Ancient times to mid-20th century

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Preeclampsia is a pregnancy-specific syndrome with an unknown etiology. In ancient Greece, Hippocrates first described the condition when he wrote in one of his Aphorisms that “convulsions take place from either repletion or depletion of the four humors”. He also observed the sudden and unexpected appearance of maternal convulsions. The word “eclampsia” was attached from the Greek for “lightning”. During the Middle Ages, medical and scientific progress came to a standstill, because Christians were opposed to science and forbade human dissection. Before long, Christian influence began to decline, and Salernitana and Arabian influences increased. With this newfound freedom, anatomist and artists were able to describe accurately the female reproductive tract. In the Early Modern ages, the beneficial effect of delivery on convulsions was recognized. In addition, it was suspected that causative factors of convulsions were probably toxic agents which originated in the decomposing fetus. In the Modern Ages, the measurement and recognition of high blood pressure was made possible by the introduction of Riva Rocci’s sphygmomanometer, and proteinuria in eclamptic women was recognized. At the turn of the 19th century to the 20th, the presence of a circulating toxin of fetal origin was postulated as the cause of eclampsia. More than a century later, the toxemic theory remains the favored hypothesis.

Introduction

Preeclampsia is a hypertensive, multi-system disorder of pregnancy with unknown etiology. It is the principal cause of maternal morbidity and mortality, accounting for almost 15% of pregnancy-associated deaths (ACOG, 1996).¹⁾ Zweifel (1916) first described preeclampsia as “a disease of theories”,²⁾ and Higgins and Brennecke (1998) re-stated that “pre-eclampsia was still a disease of theories”.³⁾

At the turn of the 19th century to the 20th, the presence of a circulating toxin of fetal origin was postulated as the cause of eclampsia, and hence the disease became known as “toxemia of pregnancy”. It is now widely accepted that preeclampsia is associated with abnormal implantation, which is believed to result in relative placental ischemia. Although its management has been developed according to evidence-based medicine, treatment only addresses the symptoms and delivery remains the only cure.

Past hypotheses and scientific contributions have influenced the current understanding of the pathophysiology of preeclampsia and have guided its management strategies and classification criteria. Understanding past and current theories regarding the etiology and pathophysiology of preeclampsia will contribute to the evolution of future work.

Ancient times

Theories on disease causation

Puerperal convulsions may have been recognized in ancient Chinese, Indian, and Greek treatises, some dating back 4,500 years.^{4,5)} In ancient Greece, from the late 5th century B.C. to the early 4th century B.C., the Hippocratics used the theory of four humors to describe the cause of illness and disease. They believed that the body was made up of four humors (fluids); namely, blood, phlegm, yellow bile, and black bile. According to them, health

depended on a balance of the humors and any imbalance resulted in illness.^{6,7)}

Hippocrates first described the condition when he wrote in one of his Aphorisms that “convulsions take place from either repletion or depletion”.⁸⁾ He also observed the sudden and unexpected appearance of maternal grand mal seizures, which might occur when preeclampsia progresses to eclampsia. The word “eclampsia”, derived from the Greek “*Εχλαμνιες*,” for “lightning”, came to be used afterward.

The danger of convulsions during pregnancy was mentioned in ancient Egyptian and Greek medical records. The convulsions were believed to be caused by poison. It was believed for many centuries that preeclampsia was a seizure disorder unique to pregnancy, but during the last 200 years, this view of the disease has changed drastically and we now know that it is not only a convulsive disorder.⁹⁾

Management

Because the disease was believed to result from an imbalance of the four humors, treatment was focused on the restoration and maintenance of the internal balance. Remedies to restore the internal balance included altered diets, purging, and bloodletting.

Middle Ages & the Renaissance (A.D. 500–1600)

Theories on disease causation

During the Middle Ages, medical and scientific progress came to a standstill, though Aetios in the 6th century A.D. noticed that “the pulse is strong and swollen” in pregnant women with convulsions.¹⁰⁾ From the 5th century into the 8th, Christianity greatly hampered such progress. Christians were opposed to science and forbade human dissection.¹¹⁾ From the 8th century into the 13th, as Byzantium declined, Christian influence began to diminish, and Salernitana (Salerno, Italy) became influential. Arabian influence also increased. With this newfound freedom, anatomists and artists such as Jacopo Berengario da Capri (1460–1530), Nicolaus Massa (1499–1569), Leonardo da Vinci (1452–1519), Andreas Vesalius (1514–1564), and Fallopius (1523–1562) made accurate drawings of the female reproductive tract.⁷⁾

Early modern times (A.D. 1600–1800)

Theories on disease causation

In the 17th century, medicine continued to gain momentum and men began to explore the field of obstetrics.¹²⁾ According to Dexter and Weiss, the word “eclampsia” (meaning “sudden flash”) first appeared in 1619 in Varandeu’s treatise on gynecology.¹³⁾ Mauriceau

(1694),¹⁴⁾ the celebrated French obstetrician, was one of those whose writings helped to establish obstetrics as a specialty.¹⁵⁾ He was the first to systematically describe eclampsia and to note that primigravidas were at greater risk for convulsions compared to multigravidas.¹²⁾ As for the causes of convulsions, he attributed them to either abnormalities in lochial flow or intrauterine fetal death,¹²⁾ and he was aware that eclamptic convulsions usually ceased following delivery. Furthermore, he suspected that the causative factors were toxic agents which originated in the decomposing fetus.¹⁵⁾ Like Mauriceau, De la Motte (1722)¹⁶⁾ recognized the beneficial effect of delivery on convulsions.¹⁵⁾ Demanet (1797) noted a connection between edematous women and eclampsia, and Boissier de Sauvages (1739) distinguished eclampsia from epilepsy.¹⁷⁾

Management (Middle Ages to early modern times)

Treatment of disease during the Middle Ages and early modern times was greatly influenced by Christian beliefs. Remedies prescribed by physicians in ancient times were often replaced with charms, amulets, faith healing, miracles, and prayers.¹¹⁾ However, as time passed and Christian influence waned, remedies similar to those used to treat disease in ancient times became prominent again. In the 18th century, for example, in an attempt to decrease cerebral congestion and prevent eclampsia, Mauriceau¹⁴⁾ recommended two to three phlebotomies during pregnancy.^{12,17)}

Modern times (A.D. 1800–1900)

Recognition of hypertension and proteinuria

As for the “pre” preceding “eclampsia”, the major criterion classically used to establish the clinical diagnosis of pre-eclampsia was detection of *de novo* hypertension and proteinuria, both occurring after mid-pregnancy. Measurement and recognition of high blood pressure was historically recent. It was only after the introduction of Riva Rocci’s sphygmomanometer in 1896 that blood pressure measurements crept into clinical practice.¹⁸⁾ However, long before then, observers had recognized the hyperdynamic circulation in normal pregnancy. The Chinese had been aware of the “bounding of the pulse” during gestation over 4,500 years ago,^{4,5)} and, as previously mentioned, Aetios in the 6th century A.D. noticed that “the pulse is strong and swollen” in pregnant women with convulsions.¹⁰⁾

In the 1880s, Ballantyne¹⁹⁾ used a crude sphygmogram as proof that blood pressure increased with eclampsia. Vaquez (1897)²⁰⁾ was credited with the discovery of eclamptic hypertension.¹⁷⁾ As for proteinuria, Rayer (1840)²¹⁾ appears to have been the first to note proteinuria in eclamptic women, but Lever (1843)²²⁾ differentiated

the proteinuria associated with preeclampsia from Bright's disease. His publication preceded that of Simpson (1843),²³⁾ who published similar findings just a month after Lever's article.²²⁾

Theories on disease causation

Various theories on disease causation continued to be proposed and thoroughly discussed in the writings of 19th century physicians. Denman (1821)²⁴⁾ focused much attention on cases of labor affected by convulsions. He noted that the greatest risk of convulsions came from the uterus; that is to say, as the uterus expanded with the progress of gestation in late pregnancy, greater pressure was applied to the descending blood vessels. According to him, such an increase in pressure led to the regurgitation of blood in the head and resulted in an overload of the cerebral vessels and subsequent convulsions.

Smith²⁵⁾ challenged the theory of cerebral congestion in his work *Parturition and the Principles and Practice of Obstetrics* (1849). He believed that pregnancy was a state of increased fullness in circulation and that contractions during the second stage of labor normally interfered with the utero-placental circulation. He also believed that more cases of convulsions would be observed if such cerebral congestion occurred strongly. Furthermore, he attributed puerperal convulsions to several other causes: 1) any mechanical or emotional stimulus applied in excess to the spinal center, 2) bloodletting, 3) variations in wind, temperature, and other atmospheric changes, 4) irritation of the uterus, uterine passages, the intestinal canal, and the stomach, and 5) "toxic" elements. As for Smith's theory on "toxic" elements, he believed that preservation of health during pregnancy depended on an exponential increase in the elimination of wastes (e.g., secretions of the bowels) and debris from the maternal and fetal systems. According to his theory, failure to do so resulted in a "toxemia" in which morbid elements accumulated in the blood, causing irritation to the nervous center.²⁵⁾

As previously mentioned, the presence of a circulating toxin of fetal origin was postulated as the cause of eclampsia at the turn of the 19th century to the 20th, and hence the disease became known as "toxemia of pregnancy". More than a century later, the toxemic theory remains a favored hypothesis.²⁶⁾

At the turn of the 19th century to the 20th, the new ability to measure blood pressure led to demonstration of the association between preeclampsia and hypertension.²⁷⁾ Hypertension was often found to precede the development of eclamptic seizures.

Management

Bloodletting remained crucial in the prevention and treatment of preeclampsia-eclampsia during the early 1800s. Puzos, in his book in 1759,²⁸⁾ described convulsive

seizures in great detail and advocated venesection, enemas, and induction of delivery as treatment.

Hamilton (1781),²⁹⁾ in his work *A Treatise of Midwifery*, also suggested that the most effective cure for convulsions which came on with labor was a speedy delivery either by turning the child or by extraction with forceps. On the other hand, the use of opiates, warm baths, splashing of the face with cold water, and hastening of delivery were also recommended by Denman (1821).²⁴⁾

As the theory of disease causation shifted to the toxin theory in the late 1800s, treatment was targeted at eliminating toxins.

The first half of the 20th century

Theories on disease causation

Although researchers in the first half of the 20th century failed to uncover the etiology of preeclampsia, much progress was made in the understanding of pathophysiological changes. According to the textbook *Williams Obstetrics* by Williams (1903), preeclampsia was caused by a toxin in the circulating blood. The toxin was said to cause a microvessel thrombosis and multiple organ pathology.

Browne (1944)³⁰⁾ described the risk factors and pathogenesis of eclampsia as follows: 1) It occurs only in pregnancy or shortly after delivery. 2) It occurs chiefly in primigravidas. 3) It may occur in a hydatidiform mole where there is no fetus. 4) It is not infrequently associated with concealed accidental hemorrhage. 5) It is sometimes associated with bilateral cortical necrosis of the kidney. To these findings of Browne, it can be added 1) that preeclampsia is more common a) where there is a large amount of placental tissue, such as in a twin pregnancy, diabetic pregnancy, or that involving an obese woman and b) where there is a family tendency; 2) that there are geographic and racial differences in the incidence; 3) that previous blood transfusion reduces the incidence; and 4) that a change in partner alters the incidence.³¹⁾

From a toxin to placental ischemia

Young (1914)³²⁾ and Bartholomew et al. (1957)³³⁾ considered a placental infarct to be the source of toxemia or eclampsia with uteroplacental ischemia. This conclusion was based on years of work done between 1930 and 1960.

Obata (Japanese Society of Obstetrics and Gynecology, 1920) reported that eclampsia was caused by a placental toxin when the power with which maternal serum counteracted the placental toxin declined. According to Magara (1960),³⁴⁾ a degenerated placenta produced a toxic vasoconstrictor polypeptide which he thought to be the trigger of toxemia. Kaku (1953)³⁵⁾ presented a theory of allergy, reporting that he had found antigenicity in

the existing polysaccharide of a degenerated placenta. However, no pressor substance was separated from the degenerated placenta in preeclampsia. Meanwhile, involvement of the kidney was also observed, since women who had died from eclampsia also had a unique form of glomerular endotheliosis.³⁶⁾

Placental ischemia

Page (1939)³⁷⁾ first noted that placentas from toxemic women appeared to be poorly perfused and denied the presence of a toxin for preeclampsia. Today we know that a consistent feature associated with poor perfusion is defective trophoblast invasion of the myometrial portion of the spiral arteries in early pregnancy.^{38,39)}

Ogden et al. (1940)⁴⁰⁾ found that hypertension could be caused in dogs by partially clamping the abdominal aorta below the level of the renal arteries. However, they found no rise in blood pressure if the pregnant uterus had been previously removed. Bastiaanse et al. (1950)⁴¹⁾ found that there was a rise in blood pressure in pregnant animals whose uterine arteries were partially clamped after the ovarian arteries had been ligated. There was no rise in blood pressure in non-pregnant animals treated similarly, and they concluded that it was placental hypoxia rather than uterine hypoxia which caused the rise in blood pressure.³¹⁾

The relationship between uterine ischemia and a rise in blood pressure was continuously studied in the latter half of the 20th century. When Kumar (1962)⁴²⁾ ligated the ovarian arteries and partially clamped the uterine arteries of dogs in late pregnancy, they developed hypertension. Pregnant rabbits which had a Z-shaped suture inserted in the placenta by Berger and Cavanagh (1963)⁴³⁾ developed hypertension. In addition, when plasma from hypertensive animals was infused into normal rabbits, the latter developed hypertension, proteinuria, and oliguria, and it was concluded that a pressor substance was released from placental ischemic tissue.

Constriction of the aorta below the level of the renal arteries in the pregnant dog, rabbit, and monkey caused hypertension and proteinuria,^{44–46)} and the authors found evidence of a renal lesion similar to that found in clinical preeclampsia. Furthermore, animal models that have successfully reproduced at least hypertension have involved mechanically reducing placental blood flow.^{47,48)}

It can be concluded from most of these animal studies that placental ischemia can cause hypertension and proteinuria in experimental models such as rabbits, dogs, and primates. This may provide evidence that preeclampsia in humans is caused by placental ischemia.

Overdistension of the uterus and subsequent placental ischemia

Overdistension of the uterus and subsequent placental

ischemia have been suggested as the cause of preeclampsia and it is frequently observed that amniotomy reduces the blood pressure in cases of preeclampsia. Polyhydramnios is also often associated with toxemia (the incidence of toxemia in polyhydramnios vs. normal pregnancy: 13% vs. 4%).⁴⁹⁾ On the other hand, polyhydramnios is not associated with a high incidence of preeclampsia.⁵⁰⁾

Sophian^{51,52)} speculated on the presence of a “Utero-Renal Reflex” associated with toxemia. Furthermore, Moriyama (*Acta Obstetrica et Gynecologica Japonica*, 1958) suggested a relationship between toxemia and kidney sympathetic activation. Takahashi (Japan Society of Obstetrics and Gynecology, 1964) noticed that increased intrauterine pressure forced sympathetic activation. However, no direct investigation has been made as to the mechanisms by which increased intrauterine pressure elevates blood pressure and decreases renal and placental blood flow.

In the latter half of the 20th century (1988), it was recognized that increasing the intrauterine resting tonus induced hypertension concomitant with decreasing placental and renal blood flow (measured by the thermocouple method or electromagnetic flowmeter).⁴⁷⁾

Disease classification

Following the discovery of a practical method for taking blood pressure, Vaquez (1897)²⁰⁾ showed that arterial hypertension was a major sign of eclampsia and that it preceded the convulsions. Proteinuria had been previously shown to precede the convulsions. Thus arose the concept of “pre-eclampsia” – that is, the syndrome consisting of hypertension, proteinuria, and certain other symptoms which occur prior to the eclamptic attack. It was soon discovered that preeclampsia was much more common than eclampsia. It was also noted that some women had high blood pressure before, during, and after delivery. While clearly not toxemias, these cases were identified as essential hypertension and added to the list of toxemias.

According to Chesley (1978),⁵³⁾ the “pre-eclamptic” state was not included in textbooks until 1903. Furthermore, restriction of preeclampsia-eclampsia to the obstetric definition was not observed until 1961. According to the classification set forth by the American Committee on Maternal Welfare (1952), toxemias of pregnancy included acute toxemia of pregnancy (preeclampsia and eclampsia), chronic hypertensive disease with pregnancy, and unclassified toxemia. In the 13th edition of *Williams Obstetrics* (1966), preeclampsia-eclampsia fell under the category of toxemias of pregnancy.

Management

From the end of the 19th century to the beginning of the

20th century, two very different approaches were taken in the treatment of eclampsia. According to Chesley, physicians in Germany and the Netherlands advocated aggressive management (e.g., prompt abdominal or vaginal cesarean section), but the associated maternal mortality rates were extremely high. As a result, more conservative management gained popularity and was widely used up until the 1930s.^{17,53} Physician pioneers of this conservative method included Tweedy of Dublin and Stroganoff of Russia.^{7,15}

Tweedy's rationale for conservative management¹⁵ was rooted in the belief that hastening labor and delivery increased the occurrence of convulsions through the induction of reflex stimulation. Physicians were to abstain from vaginal examinations, abdominal palpation, massage of the kidneys, cold blasts of air, and dilatation of the cervix in an effort to mitigate the risk of reflex stimulation. In contrast, his management plan revolved around patient sedation and included large doses of morphine. However, if a patient went into labor, he believed that the application of forceps was permissible given that the os would safely permit their application.¹⁵

Because convulsions disrupted the functions of the heart, lungs, kidneys, and liver, Stroganoff's main objective was to eliminate convulsions.¹⁵ All examinations and treatments were performed under light anesthesia and sensory stimuli were reduced by keeping the patient's room dark and quiet.¹⁷ Morphine and chloral hydrate were administered to keep patients sedated and to decrease the frequency of convulsions. To restore respiratory function, oxygen was administered. To restore cardiac function, digitalis was administered if the pulse was found to be rapid and weak after a seizure.^{15,17} Labor was to progress naturally and once a woman's cervix had dilated to six centimeters, the membranes were artificially ruptured.¹⁷

In addition to the diverse approaches to the management of preeclampsia-eclampsia in the 20th century, the use of magnesium sulfate was introduced. Although a mainstay of current treatment, it was not until 1906 that Horn first used magnesium sulfate to manage preeclampsia-eclampsia.¹⁷ During the 1920s, the parenteral use of magnesium sulfate in the treatment of preeclampsia-eclampsia was popularized by Lazard⁵⁴ and Dorsett⁵⁵. In particular, Lazard's work demonstrated that treatment with intravenous magnesium sulfate was both efficacious and safe. Later on, Stroganoff⁵⁶ reported 200 cases of eclampsia treated with magnesium sulfate.

Summary

The word "eclampsia" derives from the Greek term for "lightning", and first appeared in 1619 in Varandeu's treatise on gynecology. The danger of convulsions during

pregnancy was mentioned in ancient Egyptian and Greek medicine. The convulsions were believed to be caused by poison. They were also believed to result from an imbalance of the four humors.

During the Middle Ages, medical and scientific progress came to a standstill because Christians were opposed to science and forbade human dissection. However, Aetios in the 6th century A.D. noticed that "the pulse is strong and swollen" in pregnant women with convulsions. Before long, Christian influence began to decline, and Salernitana (Salerno, Italy) became influential. Arabian influence also increased. With this newly founded freedom, anatomists and artists made accurate drawings of the female reproductive tract.

Mauriceau (1694) and De la Motte (1722) recognized the beneficial effect of delivery on convulsions. In addition, Mauriceau suspected that the causative factors were toxic agents which originated in the decomposing fetus.

Measurement and recognition of high blood pressure were enabled by the introduction of Riva Rocci's sphygmomanometer in 1896. Following this, blood pressure measurements crept into clinical practice. As for proteinuria, Rayer (1840) appears to have been the first to note proteinuria in eclamptic women.

Denman (1821) noted that the greatest risk of convulsions came from the uterus; that is to say, as the uterus expanded with the progress of gestation in late pregnancy, greater pressure was applied to the descending blood vessels. According to Denman, such an increase in pressure led to the regurgitation of blood in the head and resulted in an overload of the cerebral vessels and subsequent convulsions. Smith (1849) believed that pregnancy was a state of increased fullness in circulation, and that, as a result, more cases of convulsions would be observed if such congestion occurred strongly.

At the turn of the 19th century to the 20th, the presence of a circulating toxin of fetal origin was postulated as the cause of eclampsia, and hence the disease became known as "toxemia of pregnancy". More than a century later, the toxemic theory remains a favored hypothesis. According to the textbook *Williams Obstetrics* of Williams (1903), preeclampsia was caused by a toxin in a circulating blood. The toxin was said to cause a microvessel thrombosis and multiple organ pathology.

Page (1939) first noted that the placenta from toxemic women appeared to be poorly perfused and denied the presence of a toxin for preeclampsia. Recent studies have focused on placental ischemia and vascular endothelial dysfunction as underlying factors in the pathogenesis of preeclampsia.

Conflict of interest

None.

References

- American College of Obstetricians and Gynecologists 1996, Hypertension in pregnancy. American College of Obstetricians and Gynecologists Technical Bulletin. 1996; 219: 1–8.
- Zweifel P. Eklampsie. In: Dederlein A. ed. *Handbuch der Geburtshilfe*. Wiesbaden, Bergmann, 1916; 2: 672–723.
- Higgins JR, Brennecke SP. Pre-eclampsia-still a disease of theories? *Curr Opin Obstet Gynecol*. 1998; 10: 129–133.
- Lindheimer MD. Historical perspective. Clinical Review. American College of Obstetricians and Gynecologists. 2013; January–February: 24–35.
- Lindheimer MD, Roberts JM, Cunningham FG, Chesley LC. eds. *Chesley's Hypertensive Disorders in Pregnancy* (3rd edn). Boston: Academic Press, 2009.
- Demand N. ed. *Birth, Death, and Motherhood in Classical Greece*. Baltimore: John Hopkins Univ. Press, 1994.
- Bell MJ. A historical overview of preeclampsia-eclampsia. *J Obstet Gynecol Neonatal Nurs*. 2010; 39: 510–518.
- Salas SP. What causes pre-eclampsia? *Baillieres Best Pract Res Clin Obstet Gynaecol*. 1999; 13: 41–57.
- Page NM, Lowry PJ. Is 'pre-eclampsia' simply a response to the side effects of a placental tachykinin? *J Endocrinol*. 2000; 167: 355–361.
- Ricci J. ed. *Aetios of Ameda: The Gynecology and Obstetrics of the 6th Century AD* (Translation). Philadelphia: Blakiston, 1950; Chapters 22–23.
- Cianfrani T. A Short History of Obstetrics and Gynecology. Springfield, IL, Thomas Books, 1960.
- McMillen S. Eclampsia. In: Kiple KF. ed. *The Cambridge Historical Dictionary of Disease*. New York: Cambridge Univ. Press, 2003; 110–112.
- Dexter L, Weiss AB. eds. *Preeclamptic and Eclamptic Toxemia of Pregnancy*. Boston: Little, 1941.
- Mauriceau F. ed. *Traité des maladies des femmes grosses et de celles qui sont accouchées*. Paris: d'Houry, 1694.
- Speert H. ed. *Obstetric and Gynecologic Milestones: Essays in Eponymy*. New York: Macmillan Company, 1958.
- De la Motte G. ed. *Traité complet des accouchemens naturels, non naturels, et contre nature, expliqué dans un grand nombre d'observations et de réflexions sur l'art d'accoucher*. Paris: 1722.
- Chesley LC. History and epidemiology of preeclampsia-eclampsia. *Clin Obstet Gynecol*. 1984; 27: 801–820.
- Booth J. A short history of blood pressure measurement. *Proc R Soc Med*. 1977; 70: 793–799.
- Ballantyne JW. Sphygmographic tracings in puerperal eclampsia. *Edinburgh Med J*. 1885; 30: 1007–1020.
- Vaquez N. De la pression artérielle dans l'éclampsie puerpérale. *Bulletin de la Société médicale des hôpitaux de Paris*. 1897; 119: 14.
- Rayer PF. ed. *Traité des maladies des reins et des altérations de la sécrétion urinaire*. Paris: Bailliére, 1840; 1837–1841.
- Lever J. Cases of puerperal convulsions with remarks. *Guy's Hospital Report*. London. 1843; 2: 495–517.
- Simpson JY. Contributions to the pathology and treatment of the uterus. *London and Edinburgh Mon J Med Sci*. 1843; 3: 1009–1027.
- Denman T. ed. *An Introduction to the Practice of Midwifery*. New York: E. Bliss & White, 1821.
- Smith WT. ed. *Parturition and the Principles and Practice of Obstetrics*. Philadelphia: Lea & Blanchard, 1849.
- Kenny LC, Baker PN. The etiology of preeclampsia. In: Belfort MA, Thornton S, Saade GR. eds. *Hypertension in Pregnancy*. New York: Basel, Marcel Dekker Inc., 2003; 7–36.
- Cook HW, Briggs JB. Clinical observations on blood pressure. *Johns Hopkins Hospital Reports*. 1903; 11: 452–534.
- Puzos N. ed. *Traité des Accouchemens*. Paris: Desaint & Saillant, 1759.
- Hamilton A. ed. *A Treatise of Midwifery*. London: J Murray, 1781.
- Browne FJ. The significance of signs and symptoms in toxemia of pregnancy. *Edinburgh Med J*. 1944; 51: 449.
- MacGillivray I. ed. *Pre-eclampsia: The Hypertensive Disease of Pregnancy*. London: WB Saunders, 1983; Chapter 12.
- Young J. The etiology of eclampsia and albuminuria and their relations to accidental haemorrhage. *Proc R Soc Med*. 1914; 7: 307–348.
- Bartholomew RA, Colvin ED, Grimes WH, Fish JS, Lester WM. Factors pertinent to the etiology of eclamptogenic toxemia. A summation of previous observations 1930–1955. *Am J Obstet Gynecol*. 1957; 74: 64–84.
- Magara M. On the pathogenic power of a placental extract. An experimental and clinical study of the etiology of pregnancy toxemia. *Gynecol Obstet (Paris)*. 1960; 59: 478–493.
- Kaku M. Placental polysaccharide and the aetiology of toxemia of pregnancy. *J Obstet Gynaecol Br Emp*. 1953; 60: 148–156.
- Bell ET. Renal lesions in the toxemias of pregnancy. *Am J Pathology*. 1932; 8: 1–42.
- Page EW. The relation between hydatid moles, relative ischemia of gravid uterus, and the placental origin of eclampsia. *Am J Obstet Gynecol*. 1939; 37: 291–293.
- Pijnenborg R, Dixon G, Robertson WB, Brosens I. Trophoblastic invasion of human decidua from 8–18 weeks of pregnancy. *Placenta*. 1980; 1: 3–19.
- Pijnenborg R, Bland JM, Robertson WB, Dixon G, Brosens I. The pattern of interstitial trophoblastic invasion of the myometrium in early human pregnancy. *Placenta*. 1981; 2: 303–316.
- Ogden E, Hildebrand OJ, Page EW. Rise in blood pressure during ischemia of the gravid uterus. *Proceedings of the Society of Experimental and Biological Medicine*. 1940; 43: 49.
- Bastiaanse NA, Van B, Mastboom JL. Ischemia of the gravid uterus as a probable factor in the causation of toxemia. In: Hammond J, Browne FJ, Wolstenholme GEW. eds. *Toxaemias of Pregnancy, Human and Veterinary*. London: Churchill, 1950; 182.
- Kumar D. Chronic placental ischemia in relation of toxemia of pregnancy. A preliminary report. *Am J Obstet Gynecol*. 1962; 84: 1323–1329.
- Berger M, Cavanagh D. Toxemia of pregnancy: the hypertensive effect of acute experimental ischemia. *Am J Obstet Gynecol*. 1963; 87: 293–305.
- Abitbol MM, Pirani CL, Ober WB, Driscoll SG, Cohen MW. Production of experimental toxemia in the pregnant dog. *Obstet Gynecol*. 1976; 48: 537–548.
- Abitbol MM, Gallo GR, Pirani CL, Ober WB. Production of

- experimental toxemia in the pregnant rabbit. *Am J Obstet Gynecol.* 1976; 124: 460–470.
46. Abitbol MM, Ober MB, Gallo GR, Driscoll SG, Pirani CL. Experimental toxemia of pregnancy in the monkey, with a preliminary report on renin and aldosterone. *Am J Pathol.* 1977; 86: 573–590.
47. Hidaka A. Clinical and experimental studies on the pathogenesis in pregnancy induced hypertension. *Acta Obst Gynaec Jpn.* 1988; 40: 1010–1020. (In Japanese.)
48. Makris A, Thornton C, Thompson J, et al. Uteroplacental ischemia results in proteinuric hypertension and elevated sFLT-1. *Kidney Int.* 2007; 71: 977–984.
49. MacLachlan TB, Claman BA. Hydramnios: Review and report of 81 cases. *Can Med Assoc J.* 1962; 86: 106–109.
50. Jeffcoate TNA, Scott JS. Polyhydramnios and oligohydramnios. *Can Med Assoc J.* 1959; 15: 77–86.
51. Sophian J. Discussion on the aetiology of preeclampsia. *Proc R Soc Med.* 1957; 50: 790–792.
52. Sophian J. Myometrial resistance to stretch, the cause of preeclampsia. *J Obstet Gynaecol Br Emp.* 1955; 62: 37–47.
53. Chesley LC. ed. *Hypertensive Disorders in Pregnancy.* New York: Appleton-Century-Crofts, 1978.
54. Lazard EM. Preliminary report in intravenous use of magnesium sulfate in puerperal eclampsia. *Am J Obstet Gynecol.* 1925; 9: 178–188.
55. Dorsett L. Intramuscular injection of magnesium sulfate for control of convulsions in eclampsia. *Am J Obstet Gynecol.* 1926; 11: 227–231.
56. Stroganoff W, Davidovitch O. Two hundred cases of eclampsia treated with magnesium sulfate. *J Obstet Gynaec Brit Emp.* 1937; 44: 289–299.

Retracted