HISTORICAL PERSPECTIVE
The History of Preeclampsia and Eclampsia as Seen by a Nephrologist
2012 Benson and Pamela Harer Seminar on History Lecture
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ABSTRACT
This article summarizes the Benson and Pamela Harer Seminar on History presented at ACOG’s Annual Clinical Meeting held in San Diego, May 2012, and entitled the “History of Preeclampsia and Eclampsia as Seen by a Nephrologist.” As the speaker’s career has been devoted to clinical work, research, and teaching relating to the kidney, volume, homeostasis, and hypertensive disorders in pregnant women, the lecture focused on the following: When puerperal convulsions were first recognized (over 4 millennia ago), their delineation as a pregnancy specific occurrence, and the origin as well as appearance of the term eclampsia. Further discussed were recognition of the disease that preceded eclampsia (preeclampsia), the many speculations regarding what causes the disorder many still refer to as a “disease of theories,” and the hunt for specific ways to prevent and manage the disease.

The author being a nephrologist focuses only on the cardiovascular and renal aspects of the disease and the various ways these complications were treated through history, leaving the obstetric history of management appropriately to Caesar! More important, the ensuing article though labeled a history lecture, also contains digressions into pathophysiology and worse “philosophy” (a synonym for speculation) and even “views.” As this summarizes an ACOG lecture, there are occasional attempts at humor, and as the author never achieved tenure in this area (history), he hopes the reader will at least smile.

INTRODUCTION
To begin, Dr. Jim Martin, ACOG’s immediate past president (2012) deserves credit for twisting this author’s arm to accept the Benson and Pamela Harer history seminar lecture invitation, as I initially balked, noting I’m a clinician-scientist whose university frowns when your lecture topic belongs to a department whose elders have not tenured you, but accepted upon remembering an event 20+ years

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previously. Hanna Gray, the University of Chicago’s first (and as of 2012, the only) woman president addressing the elected university faculty Council, noted a large donation cited in the NY Times, to which I remarked that the only column I perused in the newspaper was the obituary. She immediately replied “I always read the obituary: I am a historian.”

Also, both acknowledgments and credits are due to the late Leon Chesley, PhD (1908–2000), a legendary preeclampsia bench and clinical investigator. He was a physiologist and honorary member of ACOG who during the great depression of the 1930s found employment at New Jersey’s Margaret Hague hospital. Curious why physicians ordered certain tests, he would leave his laboratory and observe what was happening on the ward and became for decades the foremost preeclampsia authority, and my own role model. Much of the research for this lecture was his as my own chapter devoted to history in the third edition of Chesley’s Hypertensive Disorders in Pregnancy (1) is but a small extension of the extensive one in his single authored 1976 first edition (2). Said otherwise, much of the scholarship for both lecture and article is in reality his.

The initial lecture request included a plea to focus on the history of perceived causes of preeclampsia, which immediately evoked memories of Leon Chesley’s 1976 lecture, at an invitational meeting held at the University of Chicago entitled, “False Steps in the History of Preeclampsia” (3). In it Dr. Chesley noted that the mid century literary curmudgeon H.L. Mencken had assessed the cultural level of the then 48 (US) states with criteria such as literacy, college graduates, libraries, and cultural events. In each criterion, Massachusetts, Connecticut, and New York led, while Mississippi, Arkansas, and Alabama bottomed. Characteristic of this curmudgeon author, another column church, church membership revealed an inverse relation. Then someone added a 4th column, “eclamptic deaths” and from the correlations concluded the cause of eclampsia was church membership!

But as we professionals know, correlation never proves causality. We can now proceed to the history of preeclampsia and eclampsia as seen by a nephrologist.

THE ORIGIN OF THE TERM “ECLAMPSIA” AND ITS HISTORY

Recognition of puerperal convulsions and the term eclampsia preceded the prefix “pre” as well as delineation of a specific preeclampsia syndrome by millennia. The eclamptic convulsion may have been recognized in ancient Chinese, Indian, and Greek treatises, some dating back 4,000 years (discussed in reference 1 and reference 2). Chesley quotes Galen’s 1829 suggestion that term derived from the Greek term ἑκλαμπται, that some say means lightning, perhaps related to how suddenly and unexpectedly an eclamptic convulsion may arise (1, 2). But in truth this same word was used to describe epilepsy making it doubtful the two conditions were differentiated at that time. In preparing for the lecture, and not knowing Greek, I turned to the Preeclampsia Foundation’s Executive Director, as she is a presbyter, that is a Greek priest’s wife (similar to a rebbitten in my own religion), and her scholarly husband Father Demetri confirmed Chesley’s opinion, adding “eklamp” was “koiné” or common as distinguished from classical Greek!

The next question is when did we recognize eclampsia as a specific puerperal convulsion? This appears to have occurred during the 17th century in France where the discipline of obstetrics had begun to evolve. François Mauriceau, author of leading text at that time focused on the specificity of these fits (1, 2, 4), but De Sauvages (1, 2, 5) is credited with using the term eclampsia. However, while eclampsia may be the most dramatic presentation preeclamptic disorder, a critical question is when were earlier manifestations of the disease recognized,
as the “pre” that is preeclampsia’s recognition and management is one reason eclampsia is so unusual today, especially in developed nations.

**Recognizing the “Pre” Preceding Eclampsia**

Classically, the major criteria used to establish the clinical diagnosis of preeclampsia was detection of de novo hypertension and proteinuria, both occurring after mid-pregnancy* (but how often these two observations produce incorrect diagnoses were highlighted by Fisher et al in 1981 (6) whose clinical pathological correlation studies showed that the clinical diagnosis was incorrect in ~15% of primiparas and a much larger percent of multiparous. When were these criteria recognized?

**Hypertension:** Measurement and recognition of high blood pressure is historically recent. Though Hales estimated blood pressure levels early in the 19th century, and crude methods to measure it were available in the mid 19th century, it was only after the 1896 introduction of Riva Rocci’s sphygmomanometer that blood pressure measurements crept into clinical practice (7). However, long before then observers had recognized the hyperdynamic circulation of normal pregnancy, the Chinese citing the “bounding of the pulse” during gestation over 4,500 years ago (1, 2). This was exaggerated in eclampsia, obviously reflecting hypertensive levels. In the 1880s, Ballantyne (8) used a crude sphygmmomanometer as proof blood pressure increased with eclampsia. A key question here, however, is what constitutes hypertension in pregnancy?, and here this essay digresses from history to philosophy.

Research depicting the physiological adaptations to normal gestation demonstrate that despite large increases in cardiac output, there is an even greater decrease in vascular resistance, the latter due to a striking rise in arterial compliance (9). Yet the threshold defining high blood pressure in pregnancy is 140 mm Hg systolic, and 90 mm Hg diastolic and has remained so for decades. Epidemiological data obtained >50 years ago had already demonstrated an increase in adverse outcomes when diastolic levels exceeded 80 mm Hg, while similarly increased incidences occurred in the National Institute of Child Health and Development’s Trials Network in the 1990s when systolic levels exceeded 120 mm Hg (10, 11). No wonder we also have a literature described as “normotensive eclampsia”!

**Proteinuria:** Here my nephrologist heart flutters. While nephrology is historically a relatively young subspecialty compared, for example, to cardiology, and especially obstetrics, the kidney came into prominence in the early 1800s. In fact, primary and secondary hypertensive disorders weren’t delineated from nephritis (then called Bright’s disease) until the early 1900s, the latter distinctions associated with the introduction of sphygmomanometers. That may be because glomerulonephritis frequently led to renal failure, the renal histological changes provoked by the disorder catching the pathologist’s eye. Furthermore, before effective antihypertensive therapy became available, glomerulonephritis, especially in children, not infrequently led to a convulsion, and this similarity between convulsions with Bright’s disease, and those occurring in late pregnancy was noted. In distinguishing eclampsia as a separate entity three names stand out.

Rayer, a Frenchman, in 1840 appears to have been the first to note proteinuria in eclamptic women (12), but it was an Englishman, Lever who differentiated the proteinuria associated with preeclampsia from Bright’s disease (13), his publication preceding that of a Scot, Simpson who published similar findings just a month after Lever’s article (14). Still, in the 1870s, the Library of the Surgeon General’s Office Index Catalogue in its discussion of Bright’s disease suggested

*Historically edema, once another criterion was eliminated as a diagnostic sign two decades ago, the history of which can be found in reference 1 and reference 2.
further reading in the section devoted to Puerperal Convulsions, and such allusions remained in the literature at the start of the 20th century.

Digressing once more from history to philosophy is a short note on the misuse of proteinuria in managing preeclampsia. Chatting with Dr. Queenan, a Green Journal editor, this author made the mistake of remarking, “Obstetricians know little of how the kidney handles protein and thus do not approach proteinuria correctly,” he saddled me with a review to teach a more pathophysiological approach to appraising protein excretion during gestation (15). Its key points were a) the cut off between normal and abnormal excretion 300 mg/24 h has never been accurately established, not use of the protein to creatinine ratio appropriately validated; b) up to 50% of 24-hour outpatient collections in gravidas are inaccurate; in part from a failure to apply those maneuvers that minimize the large retention and timing errors that are secondary to the physiological dilatation of the ureters; c) urinary protein excretion may change secondary functional changes; apparent increases in the amount excreted having nothing to do with disease progression; and d) nephrotic range proteinuria alone (whose literature definitions range 2–5 g/d) should not be considered “severe disease” nor the sole reason for termination of a gestation; the course of blood pressure, renal function (eg, creatinine), hematological, or liver pathology, and fetal status being the better indicators. This author does not know if such remarks should be considered historical, however it may be a unique instance of a nephrologist downgrading proteinuria!

This concludes the sections related to preeclampsia’s diagnostic criteria, but prior to discussing prediction, prevention, and treatment, let us conjecture on the history of why Americans write preeclampsia as a single word but Commonwealth friends place a dash between the pre and eclampsia (pre-eclampsia) and many journal editors are unsure of which to accept! Unfortunately, this author’s research was futile, except to reread Winston Churchill’s famous remark that the United States and England were two countries separated by a common language! Perhaps the dash represents this separation!

THEORIES OF CAUSALITY

What causes preeclampsia? This is the enigma that has long puzzled us, unfortunate as understanding the specific etiology of a disease, here one at times so devastating is often the initial step to rational and specifically directed therapies. Actually, etiological theories were covered during the President’s session that preceded the Haver Seminar on History, the take home message being that research has suddenly exploded in the 2000s and that we are approaching the day when preeclampsia will no longer be referred to as the “disease of theories.” This section focuses on the author’s personal bias that the discovery of the important role of excess increments in placental production of antiangiogenic proteins that then enter the maternal circulation explains many of the disease’s phenotypes, especially hypertension and proteinuria (reference 1 chapter 6, and 16). Still needed are the explanations of what causes this increased production, but we already have reports of therapeutic successes in animal models as well as in a small human pilot study (17, 18). Ironically as we now identify these antiangiogenic factors in maternal circulation with disease phenotypes, our ancestors may not have been so incorrect when they labeled the preeclampsia, toxemia!

To return to causality; stone plaques adorn the outside walls of Chicago Lying-In Hospital naming ancients who have enhanced knowledge in obstetrics and gynecology. One by the Mother’s Aid Pavilion is empty, reserved for the person who finds either cause or cure of preeclampsia. For years, this author told the students he lectured he had discovered the initiating cause and with all eyes
watching the screen would project a scanning electronic image of a sperm labeling it the “last human element to have a head.” However, given the exponential progress in research as of 2012, the slide (today it would be a PowerPoint slide!) is no longer projected and hopes are high.

**Predicting and Preventing Preeclampsia**

**Prediction:** How accurately can preeclampsia be predicted? The conclusion from a 2004 review by Conde-Agudelo et al. (19), produced for the World Health Organization, was that no single prediction test, when available, had the appropriate positive and negative likelihood ratios to qualify as clinically useful and that combinations of tests might be more productive. Subsequently, investigators have claimed that combinations tests, performed as early as the initial trimester, produce likelihood ratios applicable to clinical use. If this proves true, we will be in a position to offer specific preventive or treating therapies when such options become available.

Historically, let me note two prediction tests that were subsequently abandoned. One developed by my role model Leon Chesley was measurement of fractional urate clearance (Crate/GFR) (1). Although this test did not achieve the likelihood ratios for clinical use, interestingly, measuring urate levels are having a second birth, that is their levels or the amount they increase by being related more strongly with adverse outcomes in preeclampsia (20).

The second historic prediction test was introduced by Norman Gant (once president of the board that bestowed specialist certification on many reading this article!) The test was based on the claim that when gravidas changed from lateral to supine decumbency, those destined to develop preeclampsia manifested a significant rise in blood pressure (21). The test proved inaccurate, some suggesting the rise was an artifact as the cuffed arm was often above the heart when evaluating a patient positioned on her side. Of specific interest though was that Dr. Norman Gant has a strong Texas accent, and this author, always hard of hearing laughed when he heard it presented, thinking it was labeled the “roll me over test”!

**Prevention:** During the 18th century, phlebotomy was considered a cure all for about anything, and prescribing it to prevent all potential pregnancy complications was natural. The great obstetrician Mauriceau recommended two or three phlebotomies as pregnancy progressed but criticized colleagues who overdid it, one on 90 occasions. Various food regimens were also advocated (long before your patients started quoting the “Brewer diet!” high in protein, and advocated by a circle of passionate advocates). But all of them either have not been evaluated in or survived a controlled trial. However, it is the history of salt restriction, or the other extreme, salt loading, each to prevent preeclampsia that evokes considerable historic and current interest.

Historical facts relating to sodium restriction to prevent preeclampsia are extensively reviewed in an article by Eric Steegers et al. (22). The authors explain why rigid sodium restriction dominated most of the previous century, including those low-salt diets many of the mothers (or at least grandmothers) reading this sentence had to endure. In fact, when as a student I took my oral obstetrics/gynecology exam in 1960, the examiner asked what was the most important thing to insist on when counseling a pregnant woman on her diet? Seeing some hesitation, he remarked, “What was it that Abraham, sitting just outside his city gave to strangers who were about to enter?” With instant recall I said “Salt” smiled, and added “Salt restriction,” passing with honors. However, as will be detailed further on, Abraham may have been far wiser than us at that period.

As Steegers et al note, two giants behind salt restriction were Zangermeister in Germany and Dr. Snoo in the Netherlands (22). Zangermeister, probably the
The most quoted preeclampsia guru at the start of the last century, expounding a new theory, periodically believed it was water retention that led to edema and when in the brain, eclampsia. He restricted fluid, which also decreased salt intake. But De Snoo used sodium balance, published by Bar in 1907, that suggested gravidas could not excrete ingested sodium as well as nonpregnant women (cited in 22). De Snoo recommended salt restriction, an era that was to last for most of the century, and where prophylactic diuretics were also employed to prevent preeclampsia, and then the world turned upside down!

An article published in Lancet in 1958 by Robinson claimed added salt actually prevented the disease and that saline infusions could decrease a preeclamptic's blood pressure, and two decades of confusion with occasional acrimonious debate ensued (23). It was further noted that severe salt restriction also resulted in low protein and calcium intake, plus smaller neonates. Reviewers analyzing studies to determine if either salt restriction or diuretics had preventative value concluded that neither could prevent preeclampsia (24–26); data also suggested gravidas leaked sodium subtly (27), and the pendulum began to swing!

This author had joined the movement with a 1973 New England Journal of Medicine review entitled Salt and Diuretics in Pregnancy (28), which to the joy of a young academic was reprinted in the Green Journal (29). The editor noted he thought it important enough to request and permit a dual publication. The article noted that the available evidence suggested a gravida should be permitted to salt her food to taste and cautioned against diuretics. My coauthor, the late Adrian Katz, a strict constructionist, far more brilliant and scholarly than I, was appalled that neither journal had edited or removed a concluding remark that "Restriction of dietary sodium is being condemned today almost with the same fervor which it was advocated a decade ago, and numerous competent physicians remain convinced they saved the prenatal course of many a gravida by confiscating her potato chips."

The 1973 article, as well as other articles, did not immediately resolve the situation. Salt restriction continued to be advocated while prophylactic and therapeutic use of diuretics were strongly defended primarily by internists, a decade where internists and obstetricians could meet by the bedside and look at each other like a species of baboons! Simultaneously, the results of studies designed to confirm that volume loading could prevent or treat preeclampsia were negative or unconvincing. Eventually, calm reigned with most caregivers allowing their patients to salt their meals to taste and assure a healthy diet. Has this calm persisted?

While not a bona fide historian, this author knows the cliché, "History repeats itself," and it has. First, the heirs of salt restriction (their leader a nephrologist) have developed a rat model of preeclampsia based on combining injections of desoxytocicosterone with high salt intake (30). These animals develop hypertension, proteinuria, and perhaps small increases in circulating levels of antiangiogenic proteins. The rats also produce large excesses of cardiotonic bufadienolides, the prototype being marnihobafagin. For those who, like this author, have difficulty pronouncing those words, they are "digoxin-like" substances, their increased levels in human preeclampsia, to date, unconvincing. Still, results from a relatively small controlled trial where Digibind, a drug used to treat digoxin toxicity was administered to women with early preeclampsia revealed little or effect (31).

Salt loading, too, has reappeared. Dr. Mohaupt's group at the University of Bern (a nephrologist, as well) has described polymorphisms of the aldo-synthase enzyme, associated with decreased aldosterone production during gestation (32). Such women are also prone to develop preeclampsia. He has further utilized a rat model to explain how decreased physiological volume expansion in early gestation may lead to preeclampsia (33). In 2012, a randomized trial of the effects of high salt diets was in progress in Switzerland.
As noted, there have been many other suggestions of how to prevent preeclampsia, but only in these last 30–40 years were any of these hypotheses subjected to rigorous randomized and blinded trials. These will not be reviewed here, but to note that such trials have in general been costly and for but two candidates, aspirin and calcium, have we evidence of even minimal benefit, often with high numbers to treat. These results are mainly based on diagnostic terms rather than adverse outcomes and some criticize the statistics used to find even the most minimal benefit (34, 35). If the money had focused on pinning down mechanism we might be better off in 2012.

TREATING PREECLAMPSIA AND ECLAMPSIA

The discussion here will be limited to managing hypertension and preventing or treating the convulsion, eclampsia. Nothing will be written about obstetric management, your author, a nephrologist, relegated for 40 year but to listen to those passionate discussions of when and how to deliver, but never casting a vote!

Leon Chesley liked to quote the late Fred Zuspan, the chair who had recruited me to the University of Chicago who with Ward wrote in 1964 that historically, "She has been blistered, bled, purged, packed, lavaged, irrigated, starved, sedated, anesthetized, paralyzed, tranquilized, rendered hypotensive, drowned, been given diuretics, had mammmectomy, been dehydrated, forcibly delivered, and neglected" (36). Chesley continued noting, "many procedures could be added to the list," noting implantation of the ureters into the colon, renal decapsulation, drainage of spinal fluid, cisternal puncture, ventral suspension of the uterus, postpartum oophorectomy, and so on (1)! Chesley went on to stress that his citations weren't made in jest, as it was important to note that each of these treatments was rational in light of some hypothesis.

Let me add my own research to the levy above, noting that leeches were also tried. Helped by Debra Scarborough, the librarian who guards ACOG's precious historical library collections, we located a handwritten medical doctoral thesis by Edward Sanders written in 1876 confirming leeches had been tried.

More seriously, prior to the above through 2012 the only definitive treatment of preeclampsia has been pregnancy termination, and even then we must be vigilant for postpartum disease and instruct our patients at discharge of the possible warning signs of postpartum eclampsia (37).

Future treatments: Taking into account the historical survey above, it should be obvious that one major reason for the facetious accounts they generated has been a marked failure to adequately research and determine the cause of preeclampsia, and as noted this may be changing. That is renewed and more focused research, especially during the first decade of the 21st millennium, may have placed us on track towards rational treatment. This refers to the painstaking studies of the role of antiangiogenic proteins in producing preeclampsia phenotypes in animal models, efforts to reverse these lesions, the pairing of antiangiogenic proteins levels with adverse outcomes in women clinically diagnosed with preeclampsia, and some very preliminary therapeutic human studies.

An animal model of preeclampsia phenotypes produced by increasing levels of antiangiogenic protein was published in 2003 and confirmed (16). A study followed in 2007 that seems to have been neglected. Li and colleagues were able to reverse hypertension and proteinuria in this model, simultaneously demonstrating resolution of glomerular endotheliosis using both histological and genotyping methodology by infusing vascular endothelial growth factor-121 (VEGF) (17). More recently, in very preliminary human work, Thadani et al successfully prolonged the gestations of women with very early preeclamptic gestations using phoresis to lower the levels of the antiangiogenic protein soluble Fms-like tyrosine

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kinase-1 (sFlt1) whose maternal circulating concentrations are extremely high in the human disease (18). Still other new data have focused on the ability of relaxin, a natural hormone to stimulate VEGF production (38). I am of the opinion that were such data available in relation to another unconquered disease but one focusing on nonpregnant patients, the line of venture capitalists would stampede! But as of 2012, such studies in pregnant women were but a trickle, reflecting the history of preeclampsia research that has been and remains amongst the diseases receiving the lowest research dollar support in terms of Disability Adjusted Life Years (DALYs). This too is a sad chapter in the history of the disease. Hopefully, it will change.

**Avoiding Eclampsia or Treating the Convulsion**

Today, parenteral MgSO₄ is the treatment of choice, usually administered intravenously but it can be given intramuscularly. It is important for developing nations where intravenous (IV) equipment and proper surveillance may not be available—When did its use commence?

Chesley once remarked that historically a neurological poison was used to dispose of one’s political adversaries. Terminally it produced convulsions. Once, instead of a Democrat or a Republican, the patient turned out to be an eclamptic, and her convulsions ceased. *(No verification could be found for this story!)* What could be verified was as follows: At the start of the preceding century, tetanus was treated with parenteral Mg and its use was suggested and tried in treating puerperal convulsions. In 1925, Lazard, at Los Angeles General hospital, reported its IV use to prevent recurrent eclamptic fits (39). Of note, he acknowledged the idea came from an intern, Dr. Bogen.

The drug was then used routinely at LA Hospital, and during the ensuing decades, use of parenteral Mg firmly entered the American therapeutic armamentarium. The Parkland Group advocated an intramuscular regimen, but it eventually lost out to the IV approach championed by Fred Zuspan. However, the English and European’s resisted Mg for decades. Furthermore, the neurology community considered MgSO₄ antiquated, unproven, and inferior to either dilantin or diazepam, and strong editorial criticisms can be found in their journals during the late 1980s (40, 41).

All this changed in the 1990s after several well-performed randomized trials where Mg proved superior to both dilantin and diazepam to both avoid and prevent recurrence of eclampsia (reference 1 chapter 12, and 42-45). But debates remain; some now note that mild preeclampsias should not receive Mg, the risk of infusion-related adverse outcomes exceeding convulsions prevented (45). More recent recommendations from Great Britain with that appealing acronym “NICE,” even term use of Mg for severe disease as “recommended,” which has been interpreted by some as “optional” (46). Of course, better evidence is required, and this author has always condemned the terms “mild” and “severe” preferring the terms “less” and “more,” recalling the earlier discussion that eclampsia derives from the Greek word meaning lightning (said otherwise, never use terms that lull a caregiver into a false sense of security!)

**Closing Thoughts**

To complete this Benson and Pamela Harer discussion, one must note an historical event at the 2012 ACOG Annual Clinical Meeting. Dr. James Martin made history, as this was the first time the theme of the President’s Session was devoted to preeclampsia, including a talk on patient advocacy by a “civilian” the Executive Director of the Preeclampsia Foundation, Eleni Tsipis, who herself had experienced serious preeclampsia. Finally, an anecdote:
A special attraction on the University of Chicago campus is its Oriental Institute Museum, known for Middle Eastern archeological treasures. This author often told potential recruits their schedule had changed and they would meet the dean taking them to the Oriental institute, showing them an Egyptian mummy. The reason for this anecdote, of course, is that Benson Harper, a leading advocate of women’s health, a former ACOG president and whose family sponsors the history seminar, is also known for his collection and lectures regarding Egyptian antiquities.

Acknowledgments

Special appreciation goes to Debra J. Scarborough, MLS, AHP, History Librarian and Archivist at the American College of Obstetrician and Gynecologists. The history library hidden in the basement of ACOG headquarters was my major discovery, and future obstetric history scholars need not worry, the collection is secured from floods. Kudos too, to Gail Isenberg, our obstetrical department’s librarian, jack-of-all-trades, and a special help to illiterate nephrologists!

Annotated References

1. Lindheimer MD, Roberts JM, Cunningham FG, Chesley LC, editors. Chesley’s hypertensive disorders in pregnancy. 3rd ed. Boston (MA): Academic Press; 2009. This reference is used to support a number of the issues discussed as the text develops, but it is chapter 1, Introduction, History, Controversies, and Definitions, p. 1–23, that is primarily devoted to history.


This study is also reviewed and the area discussed more thoroughly in chapter 14 of reference 1, Hibbard JU, Shroff SG, Lindheimer MD. Cardiovascular alterations in normal and pre-eclamptic pregnancies.


This was the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke, a prospective study performed between 1958 and 1965, in which detailed data were collected from 58,000 pregnancies. Of further interest was the integration of the first group design in that they obtained funding for a study that focused on hypertension in pregnancy, from the Institute that focuses on neurological disorders, to whom the applicants underscored the fact that preeclampsia leads to convulsion! A feat in an area that for decades has remained underfunded for research in terms of Disability Adjusted Life Years (DALYs).
11. Sibai BM, Caritis SN, Thom E, Klebanoff M, McNellis D, Rocco L. et al. Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units, N Engl J Med 1993;329:1213–8. [PubMed] [Full Text] This was one of the first large multicenter trials (2,985 participants) performed in the Maternal Fetal Trials Unit where an increased incidence of preeclampsia occurred in the women whose "normal" systolic blood pressure were between 120–134 mm Hg.


16. Maynard SE, Min JY, Merchant J, Lim KH, Li J, Mondal S. et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest 2003;111:649–58. [PubMed] [Full Text] This is a "landmark" publication that has spawned a decade of research into the role of maternal levels of anti- and proangiogenic in predicting, diagnosing and determining the severity of preeclampsia.


23. Robinson M. Salt in pregnancy. Lancet 1958;1:178–81. [PubMed] [Full Text] This is probably the most cited article of those supporting liberalization of salt intake during pregnancy. The author prescribed extra "rock salt" and claimed it prevented preeclampsia, plus demonstrated cases where saline infusions decreased blood pressure in preeclamptics.

24. Daley L, Henderson-Smart DJ. Reduced salt intake compared to normal dietary salt, or high intake, in pregnancy. 1999; Joos C. 3. Art. No.: CD001687. DOI: 10.1002/14651898.CD001687. [PubMed] [Full Text] [PubMed] [Obstetrics & Gynecology]


References 24–26 are reviews that conclude that neither salt restriction nor prophylactic use of diuretics prevent preeclampsia, neither approach having a place in the management of pregnant women.

27. Bay WH, Ferris TF. Factors controlling plasma renin and aldosterone during pregnancy. Hypertension 1979;1:410–5. [PubMed] [Full Text] These authors performed balance studies noting similar sodium excretion when salt intake was markedly restricted in both third-trimester gravidas and un pregnant controls, noting similar excretion in both groups, and concluding salt handling to be similar in the pregnant and non-pregnant state. However, at this point in gestation the 3–4 mEq/day retained by the fetus should result in the gravid subject displaying significantly lower (near zero) excretion. Thus, unlike the authors, I suggest such data demonstrate a "sodium leak" in gestation.
   The article was accompanied by editorial comment asserting that this was not a “dual publication” but had been requested by the editors to assure attention by the obstetric community.  
   This was a relatively limited trial designed to treat women with early preeclampsia. There were no differences in outcomes of women receiving digoxin immune fab (Digibind) compared to those receiving placebo, yet authors highlight a barely significant higher creatinine clearance in the treated group and suggest that Digibind preserved GFR. However, the similarity of creatinine levels in both arms suggests the difference was small or perhaps artifactual, especially as all women were performing normal renal function.  
   This article was followed by one focusing on patients with compromised enzyme activity that were successfully managed with a diet high in sodium content (Nephrol Dial Transplant 2006;21:1954–7), as well as a review focusing on molecular theories that support the revival of Robinson’s 1957 observations (Med Acupunct Med 2007;28:243–54.)  
   Both Lagakos (34) and Kleshanoff (35) preach pause and restrain from an era where subgroup analysis has been used repeatedly to determine drug effects in specific groups; for example, the subgroup of chronic hypertensives in aspirin prevent trial.  
   In this review, authors underscore how often caregivers fail to instruct patients at discharge regarding signs and symptoms of postpartum eclampsia, and how few emergency room physicians may be aware of it when the patient who has consulted appears a cautionary tale re: both patient education and health care research.  
   This is an example of a campaign in neurological literature of the 1980s suggesting that MgSO4 not be used to treat eclampsia.  
   This is one of several responses including that of the late J. Prichard who introduced the intramuscular methods used at Parkland for years. Here your author politely admonished the neurologists by reminding them that the obstetric colleges and societies set standards of care for their practitioners and that failure to administer Mg might be considered substandard care (with legal implications) at that time.  
This large multicentre randomized trial was considered a milestone and proof that all women with pre-eclampsia should receive prophylactic magnesium therapy, only to be questioned several years later when reanalysis of the data suggested that while useful for more severe disease, risk of the therapy might outweigh the benefits in women with less severe (mild) pre-eclampsia.

This opinion paper led to the abandonment by many of the use of prophylactic MgSO4 in women with less severe (mild) pre-eclampsia.