Acta Scientific Women's Health (ISSN: 2582-3205)

Volume 5 Issue 9 September 2023

Review Article

The Causation of Preeclampsia: An Unresolved Question

Jaime Salvador-Moysén*, Yolanda Martínez-López and Ana Cristina Castañeda-Márquez

Academic Group of Public Health and Epidemiology, Institute of Scientific Research, Universidad Juárez del Estado de Durango, México

***Corresponding Author:** Jaime Salvador-Moysén, Academic Group of Public Health and Epidemiology, Institute of Scientific Research, Universidad Juárez del Estado de Durango, México.

DOI: 10.31080/ASWH.2023.05.0519

Received: July 07, 2023

Published: August 04, 2023

Abstract

In this article a brief review of the most important scientific advances related to preeclampsia is made from the following perspectives; clinical, epidemiological and pathophysiological. The topics addressed are located within a broad framework, it stands out to the importance that a wide diversity of geographical, socioeconomic, clinical, nutritional and psychosocial conditions have had for the expression of this health problem. The enormous advance in knowledge that has been generated in the identification of the pathophysiological processes of the disease is underlined, as well as in the existence of screening procedures with high predictive values. The paper discusses the validity of the reductionist strategies that have prevailed over time, with the purpose of identifying the causal framework of preeclampsia, although the value they have had for the identification of specific clinical, pathophysiological and molecular processes is recognized; its usefulness for addressing the causality of the disease is questioned. This critique of reductionist approaches is supported by recent scientific information. Finally, it is suggested that an Eco- epidemiological approach represents a better strategy for the identification of the causal framework of preeclampsia.

Keywords: Preeclampsia; Causality; Investigation; Eco-epidemiology; Risk Factors; Reductionism

Introduction

Preeclampsia is a disease recognized since ancient times, which is characterized by elevated blood pressure and the presence of proteinuria in pregnant women after the 20th week of gestation. This disease continues to represent a relevant public health problem in practically the entire world, mainly due to its high prevalence and its high maternal and perinatal morbidity and mortality [1,2]. Although there are various explanations for the expression of this clinical condition, there is no one that has universal acceptance and consequently the ignorance of its "causality" is recognized; ignorance that partially explains its persistence as an individual and population health problem that affects pregnant women from different regions of the planet [3]. It is important to highlight the enormous progress that exists in the knowledge of the pathophysiological mechanisms of this disease, as well as the clarification of different biochemical and molecular processes associated with its clinical expression [4], in the same way significant advances have been made in its therapeutic management [5]. From an epidemiological perspective, there are innumerable works that have identified a variety of risk factors that have been associated with preeclampsia in population groups from different geographic regions, different ethnic groups, and different socioeconomic strata [6,7]. Among the different risk factors that

have been studied, it is important to point out the following: Nutritional factors. It has been reported that supplementation with low or high doses of calcium has a protective effect against the occurrence of preeclampsia, reducing the risk of presenting it by approximately 50% [8,9]. Oxidative stress has been shown to be an important factor in the development of preeclampsia [10], the participation of vitamin C and E supplementation in reducing risk has been suggested, due to its antioxidant properties; however, the evidence reported in the literature is inconsistent regarding this reduction [11]. Likewise, vitamin D supplementation has shown participation in the prevention of preeclampsia, promoting a decrease in the concentrations of proinflammatory cytokines, since it has been described that this vitamin has a regulatory role in inflammation and an immunomodulatory effect in the placenta [12]. Folic acid has also been shown to have a protective effect by reducing homocysteine concentrations, which in high concentrations would lead to damage to the vascular endothelium of the placenta and induce apoptosis of cytotrophoblast cells, which would have substantial implications for development of placenta and therefore in the risk of presenting the disease. Long chain fatty acids and magnesium are other nutrients that have been mentioned in the preventive treatment of this disease; the evidence of their protective role is not conclusive.

Psychosocial factors. In different empirical approaches, the importance of the psychosocial environment and its influence on the health-disease process have been proven. It has been postulated that the existence of a positive psychosocial situation, a condition in which psychosocial support prevails over psychosocial stressors, represents a protective factor for the occurrence of preeclampsia. The opposite situation, that is, the occurrence of preeclampsia, has been observed when psychosocial stressors prevail over psychosocial support, this happens when there are also specific risk factors for the clinical expression of the disease [13,14]. The works carried out by Bruce McEwen regarding allostatic load, allow us to understand the unfavorable weight that adverse psychosocial conditions have in the regulatory processes of an immunological, metabolic and cardiovascular nature of individuals [15].

Pathophysiological aspects. Studies related to the pathophysiological aspects of preeclampsia are characterized by the careful elucidation carried out in the definition of the different stages of the placentation process and the clinical implications when these processes are deficient. Evidence has also been obtained proving the importance of oxidative stress, the imbalance between proangiogenic and antiangiogenic factors, and other elements such as prostacyclin and thromboxane in increasing platelet aggregation; conditions closely related to the increased risk for the expression of preeclampsia [16-19].

Epigenetic aspects. There are several studies aimed at knowing the importance of the degrees of methylation of different groups of genes with the clinical expression of preeclampsia; positive associations have been observed between specific groups of genes with the occurrence of preeclampsia. It has been described that an advantage of epigenetic studies is due to the fact that epigenetics can provide a degree of phenotypic plasticity linked to different environmental conditions, which makes it possible to make changes in gene expression, according to environmental circumstances [20,21].

Screening and diagnostic procedures. There is an important advance in the variety of psychosocial, clinical, biochemical and molecular indicators that have shown an association with the expression of preeclampsia; showing different values in their predictive capacity, it is important to point out that these indicators are not necessarily related to each other, thus the opportunity to identify pathophysiological pathways related to biological processes of the causal framework is lost [5,22].

Geographic factors. Investigations regarding preeclampsia have been carried out, comparing the clinical characteristics and risk factors of different countries, the results show important differences in epidemiological and clinical characteristics and in the outcome of the gestational process. Significant differences have also been identified in the prevalence of the disease, differences that are due in an important way to the different levels of economic development of the countries compared [6,7,23].

Definition of the problem

For decades preeclampsia has been called the disease of “theories”, this is mainly due to the results of certain observations of a clinical or biological nature, which showed association with the disease, which was interpreted as evidence of “causation” of the same, in this way new explanations or “theories” emerged, each of which claimed to have identified the “cause” of preeclampsia

[24,25]. The persistence of explanatory paradigms of a unicausal or unidisciplinary nature, which have shown their usefulness to establish causal relationships, particularly of infectious diseases, have not shown satisfactory results to establish an explanatory model of the genesis of preeclampsia. It is important to highlight that the approach to the problem from a clinical perspective, with the careful analysis of signs and symptoms, has allowed a broad and precise knowledge of the clinical nature of the disease, although it must be mentioned that this knowledge has been insufficient to be able to establish a tentative explanation of the genesis of the disease, mainly because the information that has been obtained is part of the clinical evolution of preeclampsia, not of its causality, and although attributes such as age, parity and socioeconomic level have been identified from the characterization of women with preeclampsia, these findings are they are obtained from the analysis of cases and not from a research orientation related to the genesis of the disease. With reference to indicators of a biochemical and immunological nature, they have helped to clarify the pathophysiological mechanisms of the disease in a specific way and have also made it possible to know its severity together with clinical indicators, favoring the timely intervention of therapeutic measures [19]. Although its contribution is relevant, it does not provide information that makes it possible to identify the causal framework of the disease. The studies carried out on a diversity of polymorphisms [26] have generated information that shows their association with the expression of preeclampsia, although, in the same way as with the other approaches, the knowledge generated does not transcend its level of organization and is not articulated with variables from other levels, as the clinical or the epidemiological that allows to trace a route that clarifies the causal framework of the disease. An implicit characteristic of the aforementioned approaches is their location in the black box paradigm, a paradigm that is characterized by relating, through statistical procedures, the association that exists between risk factors of a different nature with specific results, in this case preeclampsia. Despite the wealth of information obtained through several decades of study in different fields of knowledge, both clinical and molecular, reductionist and unidisciplinary research schemes have prevailed, which also have not incorporated the knowledge generated at other levels of organization, both population as clinicians.

Discussion

The advances in the clinical understanding of preeclampsia have been extraordinary, in the same way the identification of risk factors in population groups in different geographical areas, cultures, socioeconomic strata and ethnic origin [6,7,23], has made it possible to gather extensive information, which allows characterizing the patients according to risk profiles that show differences in relation to the aforementioned geographic, cultural, socioeconomic and ethnic aspects, even though the clinical expression of the disease is the same. Consistent with this approach, pregnant women with serious nutritional deficiencies or social deprivation, who live in poor communities and countries, represent risk groups for the occurrence of preeclampsia. The low prevalence of the disease in women who live in countries with a satisfactory level of socioeconomic development and who also perform physical activities during the gestational process is indicative of the importance of a favorable environment and better biopsychosocial conditions for women with gestational processes healthy. The great advance made in the understanding of the pathophysiological mechanisms of the disease that are associated with its clinical evolution, has made it possible to know indicators of the systemic alterations that occur in the patients and have also made it possible to identify some predictive factors, both of a vascular nature like biochemistry. In the more specific area of psychosocial relationships, findings have been documented that show the importance of psychosocial support as a protective element against preeclampsia and the unfavorable impact of psychosocial stressors for the occurrence of the disease, with severe clinical implications for both mother and newborn. The above represents the enormous amount of work done on preeclampsia from different perspectives. A new challenge for researchers of this health problem is the study of the epigenetic aspects that favor or cancel the expression of the disease in women who present specific risk factors. Each of the significant findings that characterize the disease, obtained with population, social, clinical, biochemical, molecular, and genetic methodological approaches, represent valuable cognitive capital that has shown its diagnostic, clinical, and therapeutic utility; they have also explained the association of preeclampsia with a diversity of risk factors, but they do not explain its causal framework. The same happens with the various "theories" that have been proposed,

which are not really "theories" but hypotheses of the disease that have generated important knowledge, although they do not explain the different paths related to the linking of the different social, epidemiological processes, cultural, ethnic, pathophysiological and molecular factors associated with the causal framework of the disease.

With the results of countless investigations carried out on preeclampsia, it has become clear that although the clinical expression of the disease is practically the same in women who suffer from it, the risk factors, living conditions and genetic aspects are different. In the same way, there is evidence that the pathophysiological routes during the development of the disease can vary according to the risk factors that are present. The foregoing suggests that there is not a single route in the causal framework of preeclampsia, for which reason its search with reductionist or unidisciplinary paradigms has been unsuccessful. The proposal of new paradigms with an Eco-epidemiological approach [27], which locate and characterize women with preeclampsia within geographic, socioeconomic, cultural, and ethnic contexts, and their articulation with the epidemiological, clinical, and genetic risk factors of sick women with the contexts of origin, it will enable the emergence of new explanatory hypotheses according to the different social, cultural and biological conditions of women with preeclampsia. It is important to underline that the scientific evidence that currently exists, does not support the generalized idea of a single causality and a single pathway in the causal framework of preeclampsia.

Conclusions

Although there are decades of research related to preeclampsia. Both clinical and cognitive interest has not diminished. It is important to underline the significant advances that exist in the following aspects of the disease: Its detailed clinical knowledge, the diversity of its pathophysiological processes, the development of screening procedures and the clarification of different molecular processes characteristic of the disease. The results of these innumerable studies have made it possible to know the characteristics of the disease in different geographical, socioeconomic, cultural, and ethnic contexts. His means enormous cognitive capital that significantly increases the possibilities of prevention and treatment of the disease. A crucial unresolved aspect is related to the causal framework of the disease, the approaches used for the clinical, pathophysiological and epidemiological knowledge of the disease that have been successful have not given fruitful results to clarify the causal route of preeclampsia. A tentative explanation for this situation is related to the use of unidisciplinary and reductionist approaches that have been used to try to solve the problem of the "causation" of the disease. It is concluded that current scientific evidence does not support the idea of a single causality and a single route in the causal framework of preeclampsia. The need to carry out approaches with integrative investigative orientations is raised, for example the Eco-epidemiological, they represent alternatives that allow the integration of knowledge from different disciplinary fields and allow the construction of explanatory hypotheses of the genesis of the disease incorporating the most important results observed in the different studies of a geographical, socioeconomic, cultural and ethnic nature that represent the contexts in which women with preeclampsia reside. The results that can be expected with these investigative approaches are represented by the emergence of innovative hypotheses that establish a variety of pathophysiological routes of preeclampsia and consequently a variety of causal routes that explain the occurrence of the disease.

Bibliography

1. Sibai B., *et al*. "Preeclampsia". *Lancet* 365 (2005): 785-797.
2. Duley L. "The Global Impact of Pre-Eclampsia and Eclampsia". *Seminars in Perinatology* 33 (2009): 130-137.
3. Jaime Salvador-Moysén., *et al*. "The Social Conditions in the Genesis of Preeclampsia". *Open Journal of Epidemiology* 4 (2014): 115-121.
4. Aune D., *et al*. "Physical activity and the risk of preeclampsia: a systematic review and meta analysis". *Epidemiology (Cambridge, Mass.)* 25 (2014): 331-343.
5. Evdokia Dimitriadis., *et al*. "Preeclampsia". *Nature Reviews Disease Primers* 9 (2023): 8.
6. Yingying Yang., *et al*. "Preeclampsia Prevalence, Risk Factors, and Pregnancy Outcomes in Sweden and China". *JAMA Network Open* 4.5 (2021): e218401.
7. Ping Shi., *et al*. "Differences in epidemiology of patients with preeclampsia between China and the US" (Review)". *Experimental And Therapeutic Medicine* 22 (2021): 1012.

8. Hofmeyr G., *et al*. "Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems". *The Cochrane Database of Systematic Reviews* 10 (2018).

9. Woo Kinshella M., *et al*. "Calcium for pre-eclampsia prevention: A systematic review and network meta-analysis to guide personalised antenatal care". *BJOG: An International Journal of Obstetrics and Gynaecology* 129 (2022): 1833-1843.

10. Takeda E., *et al*. "Stress control and human nutrition". *The Journal of Medical Investigation: JMI* 51 (2004): 139-45

11. Conde-Agudelo A., *et al*. "Supplementation with vitamins C and E during pregnancy for the prevention of preeclampsia and other adverse maternal and perinatal outcomes: a systematic review and metaanalysis". *American Journal of Obstetrics and Gynecology* 204 (2011): 503.e1-12.

12. Khaing W., *et al*. "Calcium and Vitamin D Supplementation for Prevention of Preeclampsia: A Systematic Review and Network Meta-Analysis". *Nutrients* 9 (2017): 1141.

13. SalvadorJ., *et al*. "Hipertensión inducida por el embarazo en adolescentes: un estudio multicéntrico". *Ansiedad y Estres* 11 (2005): 17-25

14. Julián Alberto Herrera. "Prevención primaria de preeclampsia: Mito o realidad?". *Colombia Médica* 4 (2015): 154-155.

15. McEwen BS. "Central Effects of Stress Hormones in Health and Disease: Understanding the Protective and Damaging Effects of Stress and Stress Mediators". *European Journal of Pharmacology* 583 (2008): 174-185.

16. Erez O., *et al*. "Preeclampsia and eclampsia: the conceptual evolution of a syndrome". *American Journal of Obstetrics and Gynecology* 226 (2022): S786-S803.

17. Arjen R Buschman., *et al*. "Pre-eclampsia Understanding clinical complexity". *Evolution, Medicine, and Public Health* (2018): 211-212.

18. J Mayrink., *et al*. "Preeclampsia in 2018: Revisiting Concepts, Physiopathology, and Prediction". *Scientific World Journal* (2018): 9.

19. Sarosh Rana., *et al*. "Preeclampsia Pathophysiology, Challenges, and Perspectives". *Circulation Research*.

20. Torres-Salazar., *et al*. "Differential Methylation in Promoter Regions of the Genes NR3C1 and HSP90AA1, Involved in the Regulation, and Bioavailability of Cortisol in Leukocytes of Women With Preeclampsia". *Frontiers in Medicine* 7 (2020).

21. Tyrka AR., *et al*. "Methylation of the leukocyte glucocorticoid receptor gene promoter in adults: associations with early adversity and depressive, anxiety and substance-use disorders". *Translational Psychiatry* 6 (2016): e848.

22. Jaime Salvador-Moysén., *et al*. "Salivary cortisol levels as a predictor of preeclampsia in adolescents". *Colombia Médica* 43 (2012): 46-53.

23. Wang W., *et al*. "Epidemiological trends of maternal hypertensive disorders of pregnancy at the global, regional, and national levels: a population-based study". *BMC Pregnancy and Childbirth* 21 (2021).

24. Dietmar Schlembach. "Preeclampsia Still a disease of theories". *Fukushima Journal of Medical Science* 49 (2003): 69-115.

25. Lopez-Llera M. "Complexity and Complicity in Eclampsia: Barriers or Bridges?" *Medical Hypotheses* 45 (1995): 591-601.

26. Aguilar-Duran M., *et al*. "Haplotype analysis of TGF-β1 gene in a preeclamptic population of northern Mexico". *Pregnancy Hypertension* 4 (2014): 14-18.

27. Mervyn Susser, Zena Stein. "Choosing a Future for Epidemiology: II. From Black Box to Chinese Boxes and Eco-Epidemiology". In. Mervyn Susser, Zena Stein. "Eras In Epidemiology". Oxford University Press (2009).