https://doi.org/10.46389/rjd-2024-1470
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2024; volume 31, issue 1, pages 93–97

Review

Inhibin-A as an early marker of moderate preeclampsia development: Complex modified therapy and its impact on placental structure

Ulyana Franchuk[1]*

[1] Department of Obstetrics and Gynecology No. 1,
I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine, Ternopil, Ukraine

*Correspondence to: Ulyana Franchuk, Department of Obstetrics and Gynecology No. 1, I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine, 46016, Ternopil, Ukraine. Phone: +380634426945; E-mail: franchuk_uya@tdmu.edu.ua

Received: 21 November 2023 / Accepted: 27 February 2024

Abstract

Hypertensive disorders during pregnancy are a significant issue in modern obstetrics. Preeclampsia complicates approximately 5% of all pregnancies worldwide. It is an important cause of complications for the mother, fetus, and newborn and can also lead to fatal consequences. Gestosis is a critical condition syndrome that occurs during pregnancy, based on a variety of sequentially developed organ dysfunctions due to insufficient perfusion-metabolic processes and the development of fetal egg structures. Gestosis, as a syndrome of multiple organ dysfunction, is necessarily associated with pregnancy and is a critical condition. Specifically, dysfunctions are not incapacity, as dysfunction is a broader concept of organ function disruption, which can be both hypo- and hyperdynamic in nature. Also, there is not enough data on late gestosis in the modern literature which supports the relevance of the diagnosis problem and choosing the optimal treatment strategy for such women. All this leads to a growing interest in the pathogenesis of this problem.

Keywords: preeclampsia, early markers, inhibin A, diagnosis, prevention.

Introduction

Preeclampsia has always been considered one of the most serious complications of pregnancy and childbirth. Centuries of research on the pathogenesis of the disease have given it the poetic name "The Great Masquerader" due to its diversity, complexity, and insidiousness. Thanks to the research of numerous authors, great importance is given to the problem of endothelial dysfunction, the combination of trophoblast invasion inhibition in the spiral arteries of the uterus, oxidative stress, microcirculation disorders and hypercoagulation. The triggering mechanism of these processes is not definitively established. It is only known that changes occur in the placenta and ultimately lead to its hypoxia and contribute to the development of placental insufficiency, spreading to the vital organs of the pregnant woman and forming specific clinical manifestations of preeclampsia. It has been proven that with early onset of gestosis, the frequency of various complications is 1.5–3.4 times higher than with its late onset [1, 2].

One of the most complex aspects of the problem of preeclampsia is establishing its cause. The main cause of gestosis may be a problem related to the fetal egg, so concepts based on the pathophysiological mechanisms of the interaction between the fetal egg and the maternal organism are the most likely to explain the etiology of gestosis. Modern research shows that preeclampsia is associated with endothelial dysfunction, inflammation, imbalance of vasoactive substances and angiogenesis, and points to genetic and epigenetic factors that may influence the risk of developing preeclampsia. Within the endocrine system at the maternal-fetal interface, the activin-inhibin-follistatin system modulates extravillous trophoblast invasion, indicating a potential role in the pathogenesis of preeclampsia.

Preeclampsia is a major factor in morbidity and mortality among pregnant women and leads to poor outcomes for both the fetus and the mother. Predicting the health outcomes for the fetus and mother will allow for early interventions to reduce further harm. Various biochemical tests, such as human chorionic gonadotropin (hCG), inhibin A, activin A, pregnancy-associated plasma protein A (PAPP-A), fetal DNA, and color Doppler ultrasound, have been studied for their ability to predict the fetal condition and maternal health outcomes; however, most of these tests are complex and expensive [3, 4].

Prediction and prevention of preeclampsia are usually based on the study of biochemical and biophysical markers and uterine artery blood flow indices based on Doppler ultrasound. In cases where the severity of preeclampsia progresses, the treatment outcomes for pregnant women are not satisfactory. Therefore, it is necessary to develop a system taking into account the adverse consequences of this condition. Disturbances in autonomic regulation play an important role in the development of hemodynamic disorders. However, there are still many unresolved issues in the pathogenesis of gestosis. This indicates that preeclampsia can still be classified as a "mysterious" disease [5]. One of the most important tasks of modern obstetrics is the search for new methods of diagnosing preeclampsia in pregnant women. Currently, the causes of this disease and the markers of its presence are not known. The progression of preeclampsia and the possibilities of treatment and prevention have yet to be sufficiently studied. The development of prognostic criteria will allow for predicting the development of preeclampsia in the late stages of pregnancy and identifying a group of patients who need special attention and supervision due to the threat of the development of this complication of pregnancy. Timely diagnosis will allow preventive measures to be taken to prevent fetal loss and, as a result, reduce the number of resuscitation procedures for newborns.

Inhibin A as an early marker for the diagnosis of moderate preeclampsia

Inhibin A is a product of the dominant follicle and corpus luteum, but the placenta is the main site of its synthesis during pregnancy. The main function of inhibin A is to restrain the synthesis and release of follicle-stimulating hormone. At the beginning of the follicular phase, the level of inhibin A is the lowest and subsequently increases, reaching a maximum value in the middle of the luteal phase. The inhibin A and estradiol levels are quite strongly correlated during the follicular phase. After the formation of the corpus luteum, its reverse development begins after a week, which leads to the release of a smaller amount of estradiol, progesterone and inhibin A. Lowering the levels of inhibin A removes its blocking effect on the pituitary gland and the release of follicle-stimulating hormone. A low level of inhibin A is characteristic of luteal phase insufficiency. In women gradually aging with a decline in ovarian reserve, a decrease in the concentration of inhibin A is observed, which makes its use as an additional marker of ovarian reserve. During the development of placental ischemia, the balance of placental markers, such as pregnancy-related plasma protein-A and inhibin A, is disturbed. During placental ischemia, the amount of the placental marker inhibin A, a heterodimer composed of alpha (α) and beta, increases (β) subunits. Varieties of the β-subunit, A and B, are also present. Inhibin affects the secretion of follicle-stimulating hormone by the pituitary gland, while activin stimulates its production. In women, these proteins are involved in processes related to pregnancy. Inhibin is produced not only by the gonads but also by the pituitary gland, adrenal glands, and the placenta. In pregnant women, inhibin appears in the blood on the ninth day after the release of the oocyte, associated with an increase in the level of β-chorionic gonadotropin. Inhibin A has the advantage of level stability, especially in the second trimester of pregnancy, so a small error in determining the gestational age does not significantly affect the accuracy of the risks. Chorionic gonadotropin stimulates the production of inhibin A. Studying the concentration of inhibin A simultaneously in maternal serum and placenta, depending on the severity of preeclampsia, has become important in diagnosing this condition. It has been established that this biomarker is of great importance in diagnosing and monitoring preeclampsia. Studies confirm the importance of inhibin A, and quantitative data indicate a direct link between it and the development of preeclampsia [6].

Abnormal levels of maternal biochemical markers used in screening have been associated with adverse pregnancy outcomes. This study aimed to evaluate whether a combination of maternal characteristics and biochemical markers in the first and second trimesters can be used to screen for preeclampsia (PE). Scientists analyzed 147 pregnancies with PE (81 full-term pregnancies, 49 premature births, and 17 with early-onset preeclampsia), 295 with gestational hypertension, and

https://doi.org/10.46389/rjd-2024-1470

166 premature births. Compared to controls, PE cases had significantly lower median MoM for PAPP-A (0.77 *vs*. 1.10, p<0.0001), PlGF (0.76 *vs*. 1.01, p<0.0001), and free β hCG (0.81 *vs*. 0.98, p<0.001) in the first trimester along with PAPP-A (0.82 *vs*. 0.99, p<0.01) and PlGF (0.75 *vs*. 1.02, p<0.0001) in the second trimester. The lowest PAPP-A, PlGF and free β-hCG in the first trimester were observed in patients whose pregnancy was complicated by preterm birth and early onset of PE. This study showed that 67% of preterm births and 76% of early-onset PE could be predicted using a combination of first-trimester PAPP-A and PlGF maternal characteristics. Accordingly, the detection rate was 58% for gestational hypertension and 36% for cases of preterm birth. First-trimester PAPP-A and PlGF levels measured for aneuploidy screening provided sufficient accuracy in identifying women at risk for early PE, allowing women at high risk for further screening and risk-reducing therapy. This combination was less accurate in predicting women with gestational hypertension or preterm delivery [7]. Among maternal serum markers, the value of inhibin A was significantly higher in women with PE than women without preeclampsia (p<0.001) [8].

In preeclampsia, inhibin A is elevated in all trimesters, whereas activin A is elevated exclusively in the late second and third trimesters. Follistatin serum levels decrease in women with preeclampsia in the late second and third trimesters. Based on the results of the analysis, Inhibin A and activin A could serve as biomarkers of early preeclampsia. Further studies are encouraged to explore the possibility of quantifying maternal serum activin A and inhibin A levels as clinical tools for early prediction of preeclampsia [9]. High inhibin-A in the first trimester leads to the occurrence of preeclampsia (AUC 0.618, 95% CI, 0.513–0.724). In the first trimester, inhibin-A shows a potential ability to predict not only the occurrence of preeclampsia before 34 weeks of gestation but also the occurrence of preeclampsia after 34 weeks of gestation. In contrast, PlGF and PAPP-A only predict the occurrence of preeclampsia after 34 weeks of gestation [10]. An increase in the level of human chorionic gonadotropin and inhibin A is associated with higher rates of stillbirth and premature birth [11].

Diagnostics of modern markers show that the concentration of alpha-fetoprotein (AFP) and inhibin A were risk factors for preeclampsia and premature birth; low concentrations of unconjugated estriol and high inhibin A were risk factors for hypertension during pregnancy; an increased concentration of human chorionic gonadotropin (hCG) was a risk factor for gestational diabetes; high AFP, low hCG, and high inhibin A were risk factors for low birth weight; low AFP and high hCG were risk factors for macrosomia [12, 13]. Taking into account the appearance of inhibin A in a pregnant woman's blood, which coincides with the release of the egg on the 9th day of fertilization, its increase occurs simultaneously with the increase in the concentration of β-hCG. Further stimulation of the production of β-hCG is carried out due to activin A, which, like inhibin A, belongs to the β-family of the transforming growth factor. It is assumed that the increased level of β-hCG stimulates the increase of inhibin A [14]. Considering the combination of serum inhibin A with maternal risk factors was useful for predicting late-onset PE. Close monitoring of these patients is recommended [15]. Given the multifactorial causation of preeclampsia, the most promising is using an extended screening model that includes a combination of data on maternal history and biophysical and biochemical markers [16]. There is a large number of contradictions that testify to the ambiguous role of these indicators in the prognosis of the development of early preeclampsia. Thus, some authors point to the low prognostic significance of markers [17]. Other studies, on the contrary, established an increase in the prognostic value of the test using these markers; however, according to the authors, it can work only in conditions of absolute knowledge of the patient's history and the course of pregnancy by trimester [18]. Endoglin, inhibin A, and PlGF have a high predictive value for preeclampsia. Quantification of pro-RLX2 cannot predict preeclampsia. Nevertheless, the potential involvement of relaxin 2/pro-RLX2 in the pathophysiology of preeclampsia requires further study [19].

Studies show that there is a correlation between the level of inhibin A and the risk of developing preeclampsia. Analysis of the content of inhibin A confirms that at values greater than 250 ng/l, the risk of late pregnancy increases, while at values less than 190 ng/l, the risk decreases. Taking into account the mechanism of the appearance of inhibin A in the blood of pregnant women, it can be assumed that the increase in the production of this marker is associated with the development of preeclampsia and a violation of the normal formation of the placenta in the early stages of pregnancy [20]. It has been studied and analyzed that the rationality of carrying out complex modified therapy of preeclampsia in women of high risk of development, taking into account early diagnostic markers, leads to the normalization of the structure of the placenta. This is confirmed by a decrease in the frequency of alternative

changes in the placental amnion, epithelium and stroma of the chorionic villi according to the results of histological examination [21].

Scientists have investigated that the value of fibronectin in the second trimester was positively correlated with severe preeclampsia and predicted 67.7% of cases of severe preeclampsia. The combination of fibronectin, inhibin A, and mean blood pressure predicted 76.7% of cases of severe preeclampsia; predictive values for combinations of fibronectin with mean arterial pressure or inhibin A were 75.4% and 74.6%, respectively. The combination with markers increased the prognostic value of fibronectin. In addition, fibronectin was more potent for the subgroups of late severe preeclampsia and severe preeclampsia without fetal growth restriction. High second-trimester maternal serum inhibin-A is significantly associated with abnormal placentation, which increases the risk of preeclampsia and PCOS, resulting in preterm birth, but not the risk of spontaneous preterm birth. In contrast, low inhibin-A levels were not associated with any common adverse pregnancy outcomes [22]. Considering the results of this study, we can conclude that the MOM of maternal serum inhibin A levels during second-stage pregnancy screening tests can predict the frequency and severity of preeclampsia in pregnant women. This is not the case in cases of hypertension during pregnancy [23]. Women with severe or early preeclampsia had the lowest levels of TGF-β1. Levels of activin A, inhibin A, sEng, and sBG were positively correlated with mean arterial pressure and proteinuria (all $P<0.01$) [24]. The relationship between late gestation on the background of metabolic syndrome and the development of placental insufficiency was revealed. Therefore, it is necessary to conduct further research to find new molecular genetic and immunological indicators of the development of preeclampsia aimed at early diagnosis and assessment of the severity of this pathology since the prognostic ability of the above-mentioned factors is insufficient [25].

Based on this review, a combination of markers should be evaluated to identify high-risk women. It is hoped that new methods for measuring multiple markers will facilitate the development of clinically effective screening programs in the future [26].

Conclusion

New methods of diagnosis and treatment, such as the use of biomarkers and anti-angiogenic drugs, are being studied to improve the detection and management of this condition. Also, in the modern literature, there needs to be more data on late gestosis, which supports the relevance of the diagnosis problem and choosing the optimal treatment strategy for such women. All this leads to a growing interest in the pathogenesis of this problem. Despite the great interest of researchers in this issue, etiology and pathogenesis remain a subject of debate at present.

Conflict of interest

The author declares no conflict of interest.

References

1. Characterization of -cell function and insulin resistance in overweight adolescents with normal glucose tolerance / M. Sun *et al.* Exp. Ther. Med. 2013. № 6 (2). P. 547-551.
2. Pre eclampsia / E. A. Steegers, P. Dadelszen, J. J. Duvekot, R. Pijnenborg Lancet. 2010. Vol. 376, № 9741. P. 631-644.
3. Chadha, A., & Tayade, S. (2022). Urinary Protein-to-Creatinine Ratio: An Indicator of Adverse Clinical Outcomes in Preeclampsia With Proteinuria. Cureus, 14(3), e23341. https://doi.org/10.7759/cureus.23341
4. Li, W., Lin, X., Chen, Y., Liu, K., Yang, W., Zeng, S., & Zhang, J. (2022). Predictive value of the second-trimester fibronectin concentration for severe preeclampsia: A prospective nested case-control study in China. The journal of obstetrics and gynaecology research, 48(7), 1721–1731. https://doi.org/10.1111/jog.15259.
5. The effects of multi mineral-vitamin D and vitamins (C+E) supplementation in the prevention of preeclampsia: An RCT / Azami M *et al.* Int J Reprod Biomed (Yazd). 2017. Vol. 15, № 5. P. 273-278.
6. Placental and maternal serum inhibin A in patients with preeclampsia and small for gestational age / Shen Z *et al.* J Obstet Gynaecol Res. 2011. Vol. 37, № 10. P. 1290.
7. Huang, T., Bedford, H. M., Rashid, S., Rasasakaram, E., Priston, M., Mak-Tam, E., Gibbons, C., Meschino, W. S., Cuckle, H., & Mei-Dan, E. (2022). Modified multiple marker aneuploidy screening as a primary screening test for preeclampsia. BMC pregnancy and childbirth, 22(1), 190. https://doi.org/10.1186/s12884-022-04514-4.
8. Kim, Y. R., Jung, I., Heo, S. J., Chang, S. W., & Cho, H. Y. (2021). A preeclampsia risk prediction model based on maternal characteristics and serum markers in twin pregnancy. The journal of maternal-fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 34(21), 3623–3628. https://doi.org/10.1080/14767058.2019.1686757.
9. Barrero, J. A., Villamil-Camargo, L. M., Imaz, J. N., Arciniegas-Villa, K., & Rubio-Romero, J. A. (2023). Maternal Serum Activin A, Inhibin A and Follistatin-Related Proteins across Preeclampsia: Insights into Their Role in Pathogenesis and Prediction. Journal

 https://doi.org/10.46389/rjd-2024-1470

of mother and child, 27(1), 119–133. https://doi.org/10.34763/jmotherandchild.20232701.d-23-00002.

10. Keikkala, E., Forstén, J., Ritvos, O., Stenman, U. H., Kajantie, E., Hämäläinen, E., Räikkönen, K., Villa, P. M., & Laivuori, H. (2021). Serum Inhibin-A and PAPP-A2 in the prediction of preeclampsia during the first and second trimesters in high-risk women. Pregnancy hypertension, 25, 116–122. https://doi.org/10.1016/j.preghy.2021.05.024.
11. Hong, S. Y., Kim, S. Y., Kim, J. H., Hong, J. Y., Sung, J. H., Choi, S. J., Oh, S. Y., & Roh, C. R. (2021). Predictive value of quad serum markers for adverse pregnancy outcome in antiphospholipid antibody syndrome. Lupus, 30(6), 981–990. https://doi.org/10.1177/09612033211001126.
12. Yue, C. Y., Zhang, C. Y., & Ying, C. M. (2020). Serum markers in quadruple screening associated with adverse pregnancy outcomes: A case-control study in China. Clinica chimica acta; international journal of clinical chemistry, 511, 278–281. https://doi.org/10.1016/j.cca.2020.10.029.
13. Yue, C. Y., Zhang, C. Y., Ni, Y. H., & Ying, C. M. (2020). Are serum levels of inhibin A in second trimester predictors of adverse pregnancy outcome?. PloS one, 15(5), e0232634. https://doi.org/10.1371/journal.pone.0232634.
14. Sibai B.M., Koch M.A., Freire S. Serum inhibin-A and angiogenic factor levels in pregnancies with previous preeclampsia and / or chronic hypertension: Are they useful markers for prediction of subsequent preeclampsia? Am. J. Obstet. Gynecol. 2008; 199: 268e1–e9.
15. Bunyapipat, P., Pruksanusak, N., Suwanrath, C., & Geater, A. (2023). Combined maternal risk factors and the Quadruple test to predict late-onset preeclampsia in pregnant Thai women. BMC pregnancy and childbirth, 23(1), 277. https://doi.org/10.1186/s12884-023-05623-4.
16. Kleinrouweler C.E., Cheong-See F.M., Collins G.S., Kwee A., Thangaratinam S., Khan K.S. Prognostic models in obstetrics: available, but far from applicable. Am. J. Obstet. Gynecol. 2016; 214 (1): 79–90. E36.
17. Hee L. Likelihood ratios for the prediction of preterm delivery with biomarkers. Acta Obstet. Gynecol. Scand. 2011; 90 (11): 1189–1199.
18. Metcalfe A., Langlois S., Macfarlane J., Vallance H., Joseph K.S. Prediction of obstetrical risk using maternal serum markers and clinical risk factors. Prenat. Diagn. 2014; 34 (2): 172–179.
19. Rehfeldt, M., Eklund, E., Struck, J., Sparwasser, A., O'Brien, B., Palomaki, G. E., Köhrle, J., Bergmann, A., & Lambert-Messerlian, G. (2018). Relaxin-2 connecting peptide (pro-RLX2 Pregnancy hypertension, 11, 124–128. https://doi.org/10.1016/j.preghy.2017.11.001) levels in second trimester serum samples to predict preeclampsia.
20. Franchuk, U., Khmil, S., & Malanchuk, L. (2023). Metabolic syndrome as a risk factor for the development of preeclampsia in pregnant women. Romanian Journal of Diabetes Nutrition and Metabolic Diseases, 30(2), 254-258.
21. Franchuk, U., Khmil, S., Orel, Y., Franchuk, M., & Malanchuk, L. (2022). Histological analysis of the placenta in patients with preeclampsia, taking into account the proposed treatment. Romanian Journal of Diabetes Nutrition and Metabolic Diseases, 29(2), 207-213.
22. Singnoi, W., Wanapirak, C., Sekararithi, R., & Tongsong, T. (2019). A cohort study of the association between maternal serum Inhibin-A and adverse pregnancy outcomes: a population-based study. BMC pregnancy and childbirth, 19(1), 124. https://doi.org/10.1186/s12884-019-2266-y.
23. Broumand, F., Lak, S. S., Nemati, F., & Mazidi, A. (2018). A study of the diagnostic value of Inhibin A Tests for occurrence of preeclampsia in pregnant women. Electronic physician, 10(1), 6186–6192. https://doi.org/10.19082/6186.
24. Xu, Y. T., Shen, M. H., Jin, A. Y., Li, H., & Zhu, R. (2017). Maternal circulating levels of transforming growth factor-β superfamily and soluble receptors its in hypertensive disorders of pregnancy. International journal of gynaecology and obstetrics: official organ of the International Federation of Gynaecology and Obstetrics, 137(3), 246–252. https://doi.org/10.1002/ijgo.12142the.
25. Franchuk, U., Khmil, S., Malanchuk, L., Franchuk, M. (2021). Application of the decision tree method to optimize the diagnosis of late preeclampsia on the background of metabolic syndrome. Polski merkuriusz lekarski: organ Polskiego Towarzystwa Lekarskiego, 49 (291), pp. 198-202.
26. Abdi, F., Aghaie, Z., Rahnemaie, F. S., & Alimoradi, Z. (2018). A Systematic Review of First Trimester Biochemical and Molecular Predictive Tests for Preeclampsia. Current hypertension reviews, 14(1), 21–28. https://doi.org/10.2174/1573402114666180416160425.

