Review Article

The Role of Biochemical Markers in the Prediction of Preeclampsia

Abstract

According to the International Society for the study of Hypertension in Pregnancy (ISSHP) preeclampsia is a disorder that affects pregnant women, and is the prime cause of maternal and neonatal deaths. This review aims to focus on the role of biochemical markers in the prediction of preeclampsia. It was found that the efficiency and accuracy heavily depended on the timeline of pregnancy, moreover, some biochemical markers are considered more accurate when accompanied with ultrasound scan. Many of these biochemical markers are measured in the first trimester, and the normal ranges in normal pregnant women and preeclamptic women differ majorly, where some are notably increased during the first trimester, opposed to others that are decreased.

Keywords

Preeclampsia, hypertension, Pregnancy, biochemical markers.

Introduction

Preeclampsia is a complex medical disorder that is characterized by a new onset of hypertension (140/90 or greater). It occurs in pregnant women at or after the 20th week of gestation, preeclampsia is accompanied with proteinuria (1). Annually preeclampsia is responsible for more than half a million of fetal and neonatal deaths, and nearly a hundred thousand of maternal deaths (2). This disorder can quickly worsen without warning signs (2). Not only that, but preeclampsia is also associated with a risk of chronic cardiovascular diseases (3).

When comparing blood pressure patterns between a healthy gestation and a preeclamptic gestation, it was found that during healthy gestation, blood pressure normally decreases at asteady rate then increases back to normal on the day of the delivery. Contrarily, in a preeclamptic gestation, blood pressure is normal in the first half of gestation then a noticeable continuous increase in blood pressure is marked untildelivery (4). As for women with an early-

onset preeclampsia, both systolic and diastolic pressures were greater than the normal ranges for normal pregnancies (5).

It was argued that the placental weight played a role in causing preeclampsia, in which smaller placental weights were deeply connected with preterm preeclampsia (36th week of gestation), and higher placental weights were connected with term preeclampsia (37-41 week of gestation) (6). Furthermore, Redman et al. proposed that oxidative stress is the leading cause of these abnormal placental weight differences (7).

The American College of Obstetricians and Gynecologists, stated that hypertension during pregnancy is classified into four categories; 1- chronic hypertension; that exists before pregnancy or begins in the first 20 weeks of gestation. 2- gestational hypertension, which is the rise of the blood pressure at rest after the 20th week of pregnancy. 3-Preeclampsia-eclampsia; preeclampsia starts with arise of blood pressure and proteinuria, then it can progress to eclampsia which is the occurrence of tonic clonic convulsions. 4- Lastly, chronic hypertension with superimposed preeclampsia (8).

One of the important ways to distinguish preeclampsia from the other lower-risk conditions of gestation and chronic hypertension is by testing for Proteinuria (9). Many methods to measure protein that is excreted in the urine, Such as the 24-hour urine collection test. Alternatively, measuring the protein-to-creatinine ratio (P/C) using a urinary dipstick is a more convenient way. The urinary dipstick is the first screening test for proteinuria. It has a good sensitivity as a screening tool for albumin loss as well (≥300 mg/day) (10). For the dipstick analysis, a positive proteinuria result is marked as a (+1) protein value, which is equivalent to >300mg of protein for the 24-hour urine collection test, or 0.3mg/dl or more in the P/C ratio (11). However, it was mentioned in an observational study that urinary dipsticks were associated with false positive results (1). Therefore, a urinary dipstick screening test is not recommended for diagnosing preeclampsia. Not only that but the P/C ratio test is high in one-third of normal pregnancies, so it is not a reliable test of proteinuria and might show false results, subsequently, it should beconsidered as screening not diagnostic tool. The 24-hour urine collection test is impractical, especially for women requiring a rapid diagnosis, but it remains standard (10).

Although many references stated that preeclampsia is associated with placental impairment and oxidative stress (7,12), Medjedovic et al. described preeclampsia as the disease of theories, because of the lack of evidence on what the primary etiologic cause is (13).

When preeclampsia progresses to eclampsia, unexpected sudden maternal seizures start to occur. The word eclampsia is derived from a Greek origin, and means lightning (14). The mother might experience complications like hemolysis, Elevated Liver Enzymes and Low Platelet Count

(HELLP) syndrome. In this case, the fetus might experience restriction of growth which leads to low weight at birth (15).

Biochemical markers are molecules that produced in the presence of a disease, either in the beginning or during the its progression (16). In the last 10 years, Preeclampsia was heavily existing in clinical research. In the search of its causes, several new factors and pathways have been described. Many of the predicted causes of preeclampsia are found to be measurable in the mother's blood (serum/plasma markers) (17). This review aims to list the biochemical markers that were under clinical research and might aid in the prediction of preeclampsia.

In the kidneys, both Glomerular Filtration Rate (GFR) and Renal Plasma Flow (RPF) start to increase reaching their highest levels by the second trimester of pregnancy, but in preeclampsia the GFR and RPF both decrease. Preeclampsia is also characterized by decreased excretion of uric acid causing hyperuricemia as well as changes in renal morphology that leads to the increase in urinary protein excretion. Changes in osmoregulation during gestation, whichresult from a decreased osmotic threshold for both thirst and vasopressin secretion lead to water retention and dilution of body fluids (18). In the brain, cerebral circulation is affected with increased permeability over the blood-brain barrier in preeclampsia. Moreover, the cerebral blood flow is altered due to impaired cerebral autoregulation. However, increased blood pressure cannot be the only reason for eclampsia and cerebral oedema (19).

Methodology

A thorough literature search was done to cover the relevant reports on biochemical markers in association with preeclampsia and its prediction. The search was in English using electronic databases like PubMed, Medline,and Google Scholar.Peer-reviewed articles published in English focusing on biomarkers of preeclampsia were included in this article. A conclusion was made out of this review summarizing the main points covered.

BIOMARKERS

1- Fetal Hemoglobin (HbF)/α1-microglobulin (A1M)

Preeclampsia is known to have two stages (20), however, the link between them is yet to be found. According to Anderson et al. (2011) (21) the efflux of Fetal Hemoglobin (HbF) might be a leading cause in the etiology of preeclampsia since heme was notably found high in preeclamptic patients (22). When accumulated in the placenta, HbF leaks into the mother's blood by causingoxidative damages in the blood-placental barrier, (23) then HbF causes vasoconstriction and endothelial damages. Not only that, but through oxidative stress, HbF can increase the kidney's permeability to macromolecules causing proteinuria. α1-microglobulin (A1M) is an antioxidant that is synthesized in the liver, its main function is binding to free

radicals and free HbF. A1M formation is directly influenced by the increase of these substances in the maternal blood, thus the levels of A1M are increased in preeclamptic patients (24). Measuring HbF/A1M ratio in the first trimester of pregnancy can be a useful screening tool for the prediction of possible preeclamptic cases.

2- Beta Human Chorionic Gonadotropin (β-hCG)

Beta human chorionic gonadotropin (β-hCG) is a hormone produced in the placenta. It is one of the first hormones which were detected in maternal blood only two days after the implantation (25). In a study by Basirat et al. (2006) (26) the levels of β-hCG were found to be high in preeclamptic patients compared to normal pregnant women. β-hCG levels are most valuable and accurate during the beginning of the second trimester (27).

3- Pregnancy-associated Plasma Protein A (PAPP-A)

Pregnancy-associated plasma protein A (PAPP-A) is a glycoprotein (28) that enhances local insulin-like growth factor (IGF) activity. IGF is important for the fetal development, the levels of this protein increase in the mother's blood with the gestational age then decrease quickly after birth (29). PAPP-A is a biochemical marker that can predict preeclampsia in the first trimester. However, it is not a specific marker by itself, but it needs to be coupled with the doppler ultrasound (30). In recent years, decreased plasma levels of PAPP-A have been reported during all the trimesters in women with preeclampsia. Additionally, a relationship between birth weight and maternal PAPP-A plasma levels has been reported (17).

4- Doppler Ultrasonography

Doppler ultrasonography is not considered as a biochemical marker. However, it is an effective method to find more biochemical markers by estimating the blood flow in blood vessels through bouncing high-frequency sound waves. The insufficient placental perfusion has led to the use of Doppler ultrasound to evaluate the velocity of the blood flow in the uterine arteries (17). Pregnancies that show abnormal results in the Doppler ultrasonography are six times more likely to develop preeclampsia (17). Many studies stated that Doppler ultrasonography was less accurate in the first trimester than in the second trimester (17). Furthermore, in a study that used doppler ultrasonography to diagnose maternal renal vasculature by measuring the blood flow in both kidneys of 40 pregnant women with a gestational age of more than 20 weeks, the velocity of the blood flow was higher in the preeclamptic women compared to the normal ones (31).However, several studies show that the combination of the measurement between Doppler ultrasound in the second trimester and the analysis of angiogenic markers have a high detection rate, mainly for the early onset preeclampsia (17).

5- Angiogenic Factors

The placental growth factor (PlGF) is a proangiogenic factor that is produced in the placenta. It improves the action of vascular endothelial growth factor-A (VEGF-A), which is essential for vascular homeostasis (32,33). PlGF can be measured in the maternal blood from the 8th week of gestation; then it is reduced progressively after the second trimester of pregnancy until delivery. However, PlGF remains persistently low in preeclampsia due to the increased levels of soluble Feline McDonough Sarcoma fms-like tyrosine kinase-1 (sFlt-1) (33-35). The sFlt-1 is an anti-angiogenic factor that increases significantly in the maternal circulation through normal pregnancy, yet it increases even more in preeclampsia (36). This protein prevents the interaction of VEGF and PlGF with receptors on the endothelial cell surface by binding to the receptor-binding domains, thus inducing endothelial dysfunction. This will lead to the decrease in circulating free PlGF and free VEGF concentrations due to the binding of sFlt-1to the endothelial receptors. (37-40). Approximately five weeks before the onset of symptoms, the circulating maternal sFlt-1 will increase. Accordingly, sFlt-1, sFlt-1/PlGF ratio, and maternal PlGF were foundto perform well in screening, predicting development, diagnosing, and monitoring established preeclampsia in the short term. Ultimately, it is preferred to measure the sFlt-1/PlGF ratio than the PlGF level alone for the reason that the level of it decreases in preeclampsia with severe features and also in the early-onset of the disease, we cannot depend on it and it's better to do the ratio. and, in cases of the severe or the early-onset of the disease, which may limit the monitoring of disease progression (32).

6- A Disintegrin and Metalloprotease (ADAM12)

A Disintegrin and Metalloprotease (ADAM12) is a zinc dependent membrane bound protease. This protease's concentration was found to be changed noticeably in many pregnancyrelated disorders (41) including preeclampsia. Liagaard et al. (2005) (42) was the first to relate ADAM12 to preeclampsia in a study showed that the concentration of ADAM12 was decreased in the first trimester in women who developed preeclampsia later. These results were confirmed by the study of Spencer et al. (2007) (43). In another study, Spencer et al. (2008) demonstrated that the concentration of ADAM12 increases in the second trimester (44). This suggestion was contradictory to the previous studies which stated that ADAM12 recorded the highest gene transcript upregulation in the preeclamptic tissue (45). Based on this study, it was concluded that ADAM12 concentration was increased in the first trimester in women who later developed preeclampsia (46).

7- Inhibin A/Pregnancy Associated Plasma Protein-A2 (PAPP-A2)

Two other biomarkers have been found to be significantly increased in the maternal circulation and placenta of preeclamptic pregnancies which are Inhibin A, that is a type of glycoprotein hormone which belongs to the transforming growth factor family. The other one is Pregnancy Associated Plasma Protein-A2 (PAPP-A2) that is a protease which regulates the availability of Insulin Growth Factor Binding Protein (IGFBP). (47,48). Women with preeclampsia/HELLP syndrome display higher levels of inhibin A and PAPP-A2, when compared with women only suspected of preeclampsia (47). Another study showed that Inhibin A levels were greater in severe preeclampsia, than in mild preeclampsia (47). Not only inhibin A and PAPP-A2 are useful alternative biomarkers for predicting adverse pregnancy outcomes, but they may also provide added value in conjunction with the established angiogenic factors sFlt-1, PlGF, and their ratio. Additionally, combining PAPP-A2 and PlGF by calculating the PAPP-A2/PlGF ratio could potentially enhance prediction accuracy beyond that of the sFlt-1/PlGF ratio (47-49).

8- 4-Hydroxyglutamate

4-Hydroxyglutamate is produced from 4-Hydroxyproline in the mitochondria, which is mainly derived from collagen. This compound has been proposed as a potential biochemical marker for predicting preeclampsia (50). Additionally, in a study by Xiaobo et al. (2019), it was found that miR-149-5p, is a single strand non-coding RNAs that consist of 22 nucleotides, it was found to regulate physiological processes such as trophoblast cell invasion, placental immune activation and platelet aggregation. However, it was observed that there was a decrease in miR-149-5p expression in preeclamptic placental tissue (51,52). In terms of the coagulation index of preeclampsia, there were significant correlations between serum levels of 4-Hydroxyglutamate and various factors. Specifically, a strong negative correlation with Partial Thromboplastin Time (PTT) and Activated Partial Thromboplastin Time (aPTT), but a positive correlation with the fibrinogen content in preeclampsia patients were found. Additionally, serum levels of miR-149-5p showed significant correlations with various coagulation factors in preeclampsia patients. There was a strong positive correlation with both PTT and APTT, but a negative correlation with the fibrinogen content (53). Furthermore, there is a correlation between the levels of 4-Hydroxyglutamate and miR-149-5p with the timing of preeclampsia occurrence. In particular, higher levels of 4-Hydroxyglutamate were associated with an earlier onset of preeclampsia, while lower levels of miR-149-5p were associated with an earlier onset of the condition as well (50,51,53). In summary, there is a high expression of 4-Hydroxyglutamate and a low expression of miR-149-5p in preeclamptic women. These markers, either alone or in combination, can be utilized for the prediction of the condition.

9- Visfatin

Visfatin is an extracellular form of the enzyme nicotinamide phosphoribosyltransferase (NAMPT). It is an adipokine that is secreted by adipose tissue, it plays an important role in Nicotinamide adenine dinucleotide (NAD+) biosynthesis by catalyzing the conversion of nicotinamide to nicotinamide mononucleotide (NMN), In a subsequent step, (NMN) can be transformed into (NAD+) (54,55,17). A cross sectional study by Hu et al. (2008) was conducted on 27 preeclampsia cases and 28 normal pregnant women both in the third trimester in addition to 28 non-pregnant women. the results of the study showed that the maternal plasma visfatin levels were crucially decreased in women with mild preeclampsia and decreased even more in women with severe preeclampsia (56). However, other studies showed the exact opposite. In Peshawar hospitals, a total of 234 pregnant women in > 20 weeks underwent blood test to measure visfatin level by (ELISA) technique, subsequently, pregnancies of hypertensive women showed increased level of serum visfatin compared to normal pregnant women (57).

10- Placental Protein-13 (PP-13)

Placental Protein-13 (PP-13) is a protein that is related to inflammatory and cell differentiation processes in the placenta (58). PP-13 serum levels were analyzed during the first trimester and showed great specificity and accuracy. However, its practicality in the second and third trimester remains unknown (58). Many studies concluded a similar outcome in assessing PP-13 in the first trimester, that is the maternal serum levels of PP-13 are significantly decreased in women who later developed preeclampsia (58-60). The study of Khalil et al. (2010) stated that coupling the assessment of PP-13 with uterine artery Doppler ultrasound during the first trimester can aid in the prediction of an early-onset preeclampsia (61).

Discussion

Based on the findings of this review, biochemical markers predict the occurrence of preeclampsia depending on the phase of pregnancy. Some biochemical markers were found efficient in the first trimester like ADAM-12 and HbF/A1M ratio, others were found more efficient in the second trimester like β-hCG. Other biochemical markers depend on other kinds of examinations to be more accurate like PAPP-A and PP-13 both of which are best accurate when accompanied with Doppler ultrasound. When comparing the ranges of the biochemical markers in preeclamptic women and normal women, some biochemical markers are significantly decreased, contrarily some are increased. While most biochemical markers are associated with the timeline of pregnancy, some are associated with the severity of the disorder like 4-Hydroxyglutamate which indicates an early onset preeclampsia. It is important to mention that symptoms accompanied with preeclampsia are most likely to disappear after birth, unless there were complications that led to severe preeclampsia or eclampsia, and other

damages in organs like the liver and the brain. Despite the findings of this review, preeclampsia still remains the disorder of theories.There is not enough evidence that concludes how to diagnose this disorder.

Conclusion: Hopefully this review aids in summarizing the latest findings regarding the role of biochemical markers in predicting preeclampsia. The continuous research on this mysterious disorder may eventually guide scientists in the future to the exact underlying cause of preeclampsia. By then most of the neonatal and maternal morbidities and mortalities due to preeclampsia and its associated complications can be avoided.

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