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A COMPLETE REVIEW–PRECISION DIAGNOSTICS TO PREECLAMPSIA BY USING DOPPLER ULTRA SONOGRAPHY, BIOSENSORS AND RAMAN SPECTROSCOPY

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ABSTRACT

Preeclampsia (PE) is a multifactorial syndrome in 3 to 5% of pregnant women that occurs as new-onset hypertension after 20 weeks of gestation. PE is a leading cause of maternal mortality and fetal morbidity in the world, causing nearly 40% of births delivered before 35 weeks of gestation. New onset of hypertension (i.e. systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg) and proteinuria (> 300 mg/24 h) is described in women with first or multiple pregnancies. There is extensive evidence that the toxic combination of hypoxia, imbalance of angiogenic and antiangiogenic factors, and inflammation results in the reduction of uteroplacental blood flow in this syndrome. Women treated for preeclampsia also have an increased risk for cardiovascular and renal diseases. Raman spectroscopy can be a suitable tool to determine biomarkers and several diseases were investigated on human body fluids such as whole blood and blood serum. The use of Doppler ultrasonography studies of the uterine arteries in the prediction of preeclampsia and intrauterine growth retardation. Preeclampsia will increase the expression of anti-angiogenic and oxidative stress molecules additionally as hyperglycosylated human chorionic gonodotrophin with a lower in the expression, proteases, placental proteins, etc. More encouraging efforts to avoid aspirin and calcium preeclampsia, but studies on modifiable risk factors, such as obesity surgery. Severe obstetric pre-eclampsia treatment focuses on blood pressure management and seizure prevention using magnesium sulfate, but the ultimate treatment remains delivery of the fetus and placenta.

KEYWORDS: Preeclampsia; hypertension; Precision Diagnostics; Raman spectroscopy; Doppler Ultrasonography; Biosensors.

1. INTRODUCTION

Pregnancy is an important period in the life of women. During pregnancy time a large amount of nutritional, metabolic, hormonal and physiological demands and guidelines are occurred. These dynamic changes in different body system lead to pregnancy- specific syndrome known as preeclampsia.[1] Preeclampsia is a pregnancy specific disorder that adversely influences the mother (by vascular dysfunction) and the fetus (by intrauterine development restriction)[2] and it has side effects like hypertension, proteinuria, renal failure, pulmonary edema, diabetes mellitus and coagulopathy (Bleeding disorder).[3]

Preeclampsia is characterized as de novo hypertension (≥ 140/90 mmHg) with substantial proteinuria (≥ 0.3 g/24 h) at or following 20 weeks gestation.[4] One of the main reasons for preeclampsia is believed to be an absence of antioxidants.[5] Free radicals or reactive oxygen species can interact with lipids and proteins which may cause lipid peroxidation and protein modification. It is recommended that the changes of lipid and protein levels are associated with oxidative stress and vascular dysfunction in preeclampsia.[6]

According to an **American College of Obstetricians and Gynecologists** (ACOG) Task Force document, there are four clinical categories of hypertension (180/120mmHg) in pregnancy: **chronic hypertension** (140/90 mmHg), **preeclampsia, eclampsia**, and **transient hypertension** (≥ 140/90 mmHg).[7,8] Among these, preeclampsia is unquestionably the most dangerous, prompting 10– 15% maternal death around the world.[9] The average frequency rate of preeclampsia is 2-8%. Nearly half of maternal deaths and more than half of fetal deaths have been reported to be due to preeclampsia worldwide, and preeclampsia raises the risk of maternal cardiovascular disease later in life.[10]

In developed nations, the maternal death rate is around 10 for each 1, 00, 000 births and approximately 10 - 15% of these deaths are due to preeclampsia. In developing nations the maternal death rate is more than 100 times the rate of developed nations. Overall ~ 5, 00,000 maternal deaths occur every year; 99% of which occur in developing countries. The United Nations has perceived this as a critical issue and has implemented targets within the UN Millennium Development Goals that are directly related to issues encompassing maternal and newborn

child mortality.[11] There is no exact data on the frequency of preeclampsia around the world, however, it is evaluated to occur in 3– 5% of pregnancies.[12] Improving pre-eclampsia prenatal administration is the development of specific prediction models that identify women at high risk of disease.[13]

Early organization of prophylactic aspirin in high- risk women before about four months' gestation development appears to reduce the risk of pre-eclampsia by 17%. Besides, there is an 8% relative risk reduction of preterm birth and a 14% decrease in fetal and neonatal death.[14] Slow discharge of nifedipine is the most prescribed drug for mild pre-eclampsia, alongside alpha-methyldopa. For the extreme type of the disease, labetalol is the suggested drug, being nifedipine and hydralazine the alternative drugs for preeclampsia.[15]

2. GENES ASSOCIATED WITH PREECLAMPSIA

The endothelial nitric oxide synthase (NOS3) represents a susceptibility gene of preeclampsia, at least in some populations, but there might be a susceptibility gene in the vicinity of the NOS3 locus (chromosome 7 to 7q36). Three genes have been examined more widely than others: the angiotensinogen gene, the factor V Leiden gene, and the methylene tetra hydrofolate reductase (MTHFR) gene. **Jeunemaitre et al.,** found an association between the M235T polymorphism of the angiotensinogen (AGT) gene (substituting a methionine for a valine on codon 235 of the protein, which may be a marker of salt sensitivity) and hypertension.[16] **Goddard et al.** detected six genes with a significative maternal-fetal genotype interaction related to Preeclampsia in IGF1, IL4R, IGF2R, GNB3, CSF1, and THBS4. These findings and others suggest a multifactorial polygenic inheritance with a genetic component in the development of this disease.[17]

2.1 Some Selected Genes and Occurrence of Preeclampsia

A Genome is a wide association study (GWAS) has disclosed susceptibility genes for preeclampsia. Some of the gene variants and interactions between genes regulating the maternal and fetal interactions are involved in preeclampsia.

3. Epidemiology of preeclampsia

Preeclampsia is a multisystemic disorder that complicates 3%–8% of pregnancies in Western nations and constitutes a major source of morbidity and mortality around the world.[18] It is a disorder of women with first pregnancy; multiparous pregnant women with another accomplice have a raised danger of preeclampsia like that of nulliparous women.[19]

3.1. Morbidity and mortality associated with preeclampsia

The World Health Organization (WHO) estimates that around the world, preeclampsia is assessed to be in charge of approximately 15 to 20% of maternal deaths every year (50,000 – 75,000). In 2002, there were roughly 41, 52,000 instances of preeclampsia that resulted in 63,000 deaths around the world. One of the United Nations Millennium Development Goals for 2015 is to reduce the maternal mortality proportion by three – quarters. Preeclampsia is related with a prenatal and neonatal death rate of 10% worldwide and represents 15% of the known causes of premature births, the increment being even up to three – fold compared to uncomplicated pregnancies.

3.2. Pathophysiology of Preeclampsia

Preeclampsia has a complex pathophysiology, the primary cause being abnormal placentation.[18] It is a systemic syndrome of pregnancy originating in the placenta.[19] Preeclampsia is characterized by placental hypoxia and/or ischemia, excessive oxidative stress, in association with endothelial dysfunction.[20] There are several key mechanisms involved that eventually lead to the clinical syndrome of preeclampsia; the immune response at the placental – maternal interface, superfacial placentation with insufficient remodeling of spiral arteries, an imbalance in angiogenic factors and oxidative stress that triggers inflammation.[21]

3.3 Recent Advances in Pathophysiology of Preeclampsia

In 2017, Warrington et al. reported that preeclampsia is an angiogenic imbalance, principally driven by the production of soluble fms-like tyrosine kinase-1 (sFlt-1), the soluble vascular endothelial growth factor (VEGF), and placental growth factor (PlGF) receptor antagonist. A number of groups have investigated the use of angiogenic factors as reliable diagnostic markers since the initial studies in which sFlt-1 was proposed as a biomarker for the diagnosis of preeclampsia.[22]

In 2015, **Duhig et al**. reported that hypertension and proteinuria were absent in 38% of women who presented with an eclampsia convulsion, demonstrating that severe maternal adverse events occur without the traditional clinical definition of preeclampsia.[23]

4. Raman Spectroscopy

In 1928, an Indian physicist Chandrashekhara Venkat Raman discovered the phenomena of inelastic scattering of light, known as the **Raman Effect.**[24] Raman spectroscopy is a non-destructive, label-free method used to determine the atomic structure of samples in a variety of states. It uses laser light to segregate between various cell and tissue types and has shown great promise *in vivo* diagnostic method.[25] Raman spectroscopy is typically sensitive to concentrations of bio-molecules such as lipids, proteins, carbohydrates, and nucleic acids.[26] Raman spectroscopy has a few highlights that are favorable for therapeutic diagnostics. It has high chemical specificity and molecular information can be acquired without requiring staining or labeling. Changes in the sub-atomic organization of biological samples as estimated by Raman spectroscopy can be utilized to

manufacture multivariate adjustment and classification models, which permit quantitative and target analysis for independent patients.[27]

4.1 Investigation of Preeclampsia using Raman Spectroscopy

In 2014, Si-Jin Chen et al. showed that: (1) the protein structure of α-helix, β-pleated sheet, and β-turn in the preeclamptic placenta is overlying, contributing to a protein structure disorder. (2) In preeclamptic placental tissue, the Raman peaks assigned to the tryptophan indole ring and phenylalanine are higher than in normal tissue. It means that the ordered structures in protein molecules of the main chain are significantly reduced, and the amino acid of side chains is damaged. (3) The PCA could give us useful help on distinguishing the Raman spectra between normal and preeclamptic placental tissues and the Raman spectroscopy presents a great potential on the mechanism research and diagnosis of placental lesions.[28]

In 2014, Lili Zhao et al., was devoted to the development of new methods for early diagnosis of preeclampsia in order to reduce maternal and infant mortality rates. Uric acid, an end product of purine metabolism, has been shown to be an effective biomarker in urine and serum samples and may be essential for the development of an early onset test for gestational hypertension (preeclampsia). Recently, an Easy Touch self-monitoring system was developed for the determination of uric acid in the blood, which realized rapid, in-home detection of uric acid.[29]

In 2013, Barbara L. Goodall et al. reported that the development for on-site real-time monitoring as an ideal non-invasive and diagnostic tool for early detection of preeclampsia based on electrochemical SERS (E-SERS) detection of uric acid in urine stimulant.[30]

In 2012, Gunay Basar et al. reported that the Department of Obstetrics and Gynaecology, Istanbul Medical Faculty, Istanbul University, Turkey. This research is the first spectroscopic study on preeclampsia by Raman. Raman spectroscopy can be an appropriate method for identifying biomarkers that can play a role in the pathophysiological mechanism of diseases. Several diseases have been studied using Raman spectroscopy on human body fluids such as whole blood and blood serum.[31]

In 1999, Tae-Woong Koo et al. reported that Surface-Enhanced Coherent Anti-Stokes Raman Scattering (SECARS) provides ultra sensitivity in molecular detection by combining the strong electromagnetic enhancements associated with SERS. As it is a label-free detection method, Surface-enhanced coherent anti-Stokes Raman scattering SECARS can be applied to a broad range of molecular detections and will serve as a new ultrasensitive tool for biomolecular studies.[32]

5. Doppler Ultrasound Sonography

Doppler ultrasonography is the main non-invasive method that does not require contrast enhancement, preparation of the patient before the examination, or radiation exposure. Doppler ultrasonography is a decent technique for screening and development, as well as for the complete diagnosis of peripheral arterial disease.[33] The capacity to identify and measure the blood flow by means of Doppler ultrasonography (US) has made this technique an irreplaceable adjunct to imaging. Doppler US is assuming a developing role in the diagnosis of the stomach, pelvic, and fetal disorders.[34]

5.1 Investigation of Preeclampsia using Doppler Ultrasound Sonography

In 2017, Cristiane Alves Oliveira et al. suggested that $MgSO_4$ has a cerebral (and retinal) vasodilator effect in women with pre-eclampsia. Ophthalmic artery Doppler is an invasive examination used to study central territory vascular flow during pregnancy. This study evaluates the ophthalmic Doppler index before and after intravenously administered MgSO4 in women with singleton pregnancies complicated by severe Preeclampsia.[35]

In 2016, Arfa Tabassum et al. reported that Doppler ultrasonography (DUS) can be used routinely for the assessment of the blood flow in uterine arteries from the third trimester. Poor trophoblast invasion of maternal vessels is characterized by the persistent diastolic notch, a defined presence beyond 24 weeks of gestation, or abnormal ratios of flow and velocity in the uterine arteries. Timely and precise anticipation of preeclampsia is essential for the wise apportioning of available resources for supervision, prevention, and management of pre-eclampsia, thus allowing for better maternal and perinatal outcomes.[36]

In 2016, Viktorija Taraseviciene et al. reported that uterine artery dopplerometry or angiogenic factor measurement is superior in diagnostics of preeclampsia. The especially great importance of angiogenic factors could be in cases of atypical preeclampsia.[37]

In 2016, Yasmin Casmod et al. investigated that Preeclampsia remains the main cause of perinatal morbidity and mortality in India. Since an abnormal Doppler flow pattern and resistance to flow in the Umbilical Artery (UA) are strong predictors of the most severe cases of preeclampsia, it is recommended that patients at high risk for these adverse pregnancy outcomes be offered ultrasound screening.[38]

In 2015, Teena Nagar et al. reported that the combination of uterine and umbilical artery Doppler is the best indicator for the prediction of preeclampsia and intrauterine growth restriction (IUGR). Diastolic notch in the uterine artery as a single parameter is better than the individual Doppler indices in the uterine artery. Absent end-diastolic flow is the best predictor of preeclampsia and poor fetal outcome. Doppler study is used for the

prediction of preeclampsia and IUGR to reduce maternal and perinatal morbidity and mortality.[39]

In 2013, Maria et al., investigated that Doppler ultrasonography vision about preeclampsia induced vascular changes in the mother, reflected as vascular changes in the uterine artery, and in the fetus, considered as alterations in umbilical and middle cerebral artery parameters; additionally, these abnormal Doppler ultrasonography measurements were disaggregated for each examined vessel. Ultrasonography indicators for the pathology and it could contribute to generate more descriptive and accurate reports during the preeclampsia evaluation using Doppler assessment.[40]

In 2013, Mallikarjunappa et al. reported that the Doppler study should be the primary imaging modality of choice for fetomaternal surveillance in PIH pts, Doppler study helps us i.e. Radiologists and OB & Gynecologists to take timely action, plan the correct treatment and counsel the parents in future deliveries. In the majority of the pts all the Doppler changes were returned to normal after bed rest & treatment.[41]

In 2012, Nazanin Farshchian et al. investigated the effect of administration of MgSO4 in severe preeclampsia cases on fetal umbilical and middle cerebral arteries (MCA) blood flow. Doppler ultrasound is a useful tool for studying pathophysiological mechanisms that can affect fetal hemodynamic status.[42]

In 2008, YU et al. investigated that Doppler ultrasound assessment of the uterine arteries is more effective in identifying severe early pre-eclampsia associated with small-for-gestational-age (SGA) than pre-eclampsia without SGA or SGA without pre-eclampsia.[43]

In 2001, Martin et al. reported that Doppler ultrasound has been demonstrated to be a reliable, non-invasive method of examining uteroplacental perfusion.[45]

In 2001, Papageorghiou et al. reported that Doppler ultrasound studies of the uteroplacental circulation have confirmed the original observation that increased impedance to flow in these vessels is associated with an increased risk for subsequent development of preeclampsia and/or FGR.[46]

In 1996, Harrington et al. reported this study supports the proposal that it is possible to identify, with uterine artery Doppler studies, a group of women at high risk of developing preeclampsia or delivering a growth-retarded baby. Early detection of disease should lead to an improved outcome, through increased surveillance and the use of prophylactic therapies such as low – dose aspirin.[47]

In 1988, Shirley A.Steel et al. investigated that Doppler ultrasound as a screening test for any degree of hypertension in pregnancy may seem somewhat disappointing, with a sensitivity of only 29% at 24 weeks in the present study and 67% at 18 weeks in the previous study. The results of this study clearly indicate that all cases of severe preeclampsia associated with IUGR can be detected by Doppler screening in early pregnancy and that those who are detected are highly likely to require clinical treatment and early intervention.[48]

6. Biosensors

A biosensor utilizes a biological component or biocatalyst to detect the presence of an analyte and a transducer to make a quantifiable signal from this interaction. Biosensor can be utilized possibly in a clinical setting; it must be highly specific for the target analyte, precise in patient samples, quick and dependable, and resistant to non-specific interactions in clinical samples. Furthermore, for certain applications, particularly in resource poor conditions, it is also desirable for the sensor to be cost - effective and simple to-utilize.[49]

6.1 Investigation of Preeclampsia using Biosensors

In 2015, Indu Pandey et al. reported that early detection or prediction of preeclampsia is imperative and non-invasive diagnostic methods based on biomarkers. L-ascorbic acid (Vitamin C) as a natural antioxidant helps to prevent oxidative stress by preventing body tissues from harmful free radicals (reactive oxygen molecules). Oxidative stress is a key feature in the development of complications in pregnancy like preeclampsia due to which vitamin c levels were significantly lower in the blood plasma of preeclamptic women.

In 2014, Pankaj Suman. Suggested that preeclampsia is an increase in the expression of anti-angiogenic molecules (soluble Fms – like tyrosine kinase protein, soluble endoglin) and oxidative stress molecules (human chorionic gonodotrophin) with a decrease in the expression of angiogenic molecules, proteases, placental proteins, etc.[50]

7. Risk Factors for Preeclampsia

Risk factors include chronic hypertension, renal disorders, obesity and insulin resistance, diabetes mellitus, pre-existing thrombophilia, family history of preeclampsia, and smoking.

7.1 Signs and Symptoms of Preeclampsia

1. Visual changes, such as consistently seeing spots or flashing lights in front of the eyes, blurred vision or being oversensitive to light
2. Severe headache
3. Swelling, especially around the ankles and feet, and in the hands and face.
4. Pain in the upper right abdomen
5. Difficulty breathing
6. Sudden nausea or vomiting in the second half of pregnancy
7. In its most severe form, seizures can occur in a pregnant woman with preeclampsia, resulting in a

condition known as "eclampsia," which is considered a medical emergency and needs immediate treatment because it can be life-threatening.

7.2 Prediction of Preeclampsia

The task force was unable to locate any evidence that accurate prediction improves maternal or fetal outcomes, despite great research interest in developing tests of biomarkers or using uterine artery Doppler velocimetry to predict preeclampsia. Recent studies using risk factors to predict preeclampsia have been only modestly successful, showing detection rates at best of 37%, with the false - positive rates of 5% to 10%.

7.3 Prevention of Preeclampsia

Multiple studies have explored potential therapies for the prevention of preeclampsia, including various antioxidant vitamins, calcium, and aspirin, as well as bed rest and activity restriction. No single therapy has proved to be overwhelmingly effective, but currently, low dose aspirin, as an antiplatelet and anti-inflammatory agent, is the favorite. The proposed mechanism is the improvement in the disruption of the prostacyclin – thromboxane balance, reducing thromboxane – mediated vasoconstriction, as well as an improvement in placental perfusion and reduction in ischemia – mediated endothelial damage.

7.4 Treatment options for preeclampsia

Delivery remains the ultimate treatment for preeclampsia. Possible treatment for preeclampsia may include:

- **Medications to lower blood pressure:** Antihypertensive drug therapy is recommended for pregnant women's with blood pressure in the range of 140/90 mm Hg. Hydralazine and labetalol are the antihypertensive drugs most commonly used in women with severe preeclampsia. Nifedipine and sodium nitroprusside are potential alternatives, but significant risks are associated with their use.
- **Corticosteroids:** Corticosteroid treatment in enhancing fetal lung maturation and temporarily improve liver and platelet function of preeclamptic women.
- **Anticonvulsant medications.** Magnesium sulfate has been widely used as a preferred anticonvulsant for women with preeclampsia.

7.5 The Millennium Development Goals

The United Nations has recognized this as a significant problem and has implemented targets within the UN Millennium Developmental Goals that are directly related to issues surrounding maternal and infant mortality. The MDGs are a commitment by the United States to establish peace and a healthy global economy by focusing on major issues like poverty, children's health, empowerment of women and girls, sustainable environment, disease, and development.

8. SUMMARY AND CONCLUSION

Preeclampsia is a common disease in pregnancy worldwide, causing maternal and fetal morbidity and mortality. Despite a better understanding of the pathophysiological mechanisms underlying the disease, the only curative treatment is delivery.[51] Delivery is the only cure for preeclampsia. Recent findings on the role of circulating antiangiogenic factors have generated great optimism for being able to predict better the disease and develop therapeutic advances.[52] Preeclampsia is a multifactorial disease, where maternal and fetal factors converge to result in a multi-component risk. No single factor has been identified as capable of determining the disease, and several are needed to trigger symptoms of PE.[53] Raman spectroscopy can provide new accurate methods in recording changes of serum protein secondary structure and concentration during normal pregnancy and preeclampsia.

The causes are multifactorial, and the disease is characterized by severe vasoconstriction, leaky capillaries, and intravascular volume contraction of endovascular and platelet dysfunction, resulting in multiorgan hypo perfusion, with the potential for significant end-organ damage, including preeclamptic seizures. In the future there is a need for multicenter studies with a large number of cases using the latest technology, such as array comparative genomic hybridization and massively parallel sequencing, to reveal the genetic changes which have occurred on the whole genome in women with preeclampsia and the HELLP syndrome.

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