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Preeclampsia Outcomes in Last Decade

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ABSTRACT

This literature review has the purpose of studying relevant scientific papers on the topic of preeclampsia from the years of 2012 to 2022. The aim is to identify current diagnosis principles as well as newly suggested diagnoses and treatment methods during each year and compare the results to each other. Also, three preeclampsia complications have been researched for each year of the decade: placental abruption, “hemolysis, elevated liver enzymes, low platelets”- syndrome or parts of it and eclampsia or use of magnesium sulfate. Methodically, scientific papers were searched for with PubMed and Google Scholar with the keywords listed below and filtered by year. Either one or more papers were chosen for a specific year and the most relevant information for this literature review was filtered out.

The results are that certain researched factors, such as soluble fms-like tyrosine kinase 1 to placental growth factor (sFlt-1/PlGF) ratio, were disagreed upon in terms of importance by different researchers throughout the years. More importantly, there are several findings that deserve to be expanded on further: including micro ribonucleic acids (microRNAs), estrogen, ceruloplasmin and the administration of 17-alpha-hydroxyprogesterone caproate (17-OHPC). As for maternal outcomes, the variation was quite high. No certain trends could be identified on an international scale.

To conclude, preeclampsia, its pathogenesis, diagnosis, and treatment have not been researched appropriately in the last decade. For the safety of pregnant women and their fetuses, the recommendation of this literature review is to continue studying the disease and its aspects.

KEYWORDS

Preeclampsia outcomes, preeclampsia, preeclampsia microRNA, preeclampsia uterine pulsatile index, preeclampsia maternal outcomes, preeclampsia sFLT-1/PlGF ratio, preeclampsia maternal and fetal outcomes

INTRODUCTION

Preeclampsia is a systemic hypertensive disorder of pregnancy that can lead to serious complications once it takes its course. It is the precursor to eclampsia, which is characterized by seizures, mostly grand mals, lasting about one minute to one minute and a half, or sudden coma (1). Being the most severe hypertensive disorder of pregnancy, it is responsible for over 70,000 maternal and 500,000 fetal deaths per year worldwide (2) and occurs in 3-7% of pregnancies (3). It most commonly presents with new-onset hypertension after the 20th week of gestation and new-onset proteinuria and may be superimposed on chronic hypertension (4). It can also develop de novo in the postpartum period. The pathogenesis of the disease possibly revolves around abnormal placentation and the consequent release of antiangiogenic factors, which presents with symptoms of high blood pressure (systolic

≥140 mmHg or diastolic ≥90 mmHg), proteinuria, edema, seizures and - in the worst case - end-organ damage and maternal or perinatal fetal death. It can be classified into subtypes by onset and severity. Early-onset preeclampsia begins before 34 weeks of gestation while late-onset preeclampsia manifests after 34 weeks. They cannot be differentiated using laboratory assessments, but they do have different clinical features. It was studied that in early-onset preeclampsia, fetal growth restriction and insufficient placental vascularization was pronounced. That could be the causative factor as to why early-onset preeclampsia meets the course of a preterm delivery and might therefore also be called early-delivery preeclampsia rather than "onset" (5).

Another subtype of preeclampsia is postpartum preeclampsia. It is believed that this type might represent subclinical or even unresolved preeclampsia (4), but it can also represent the pathology de novo (5).

When it comes to classifying according to severity, it is recommended to look at kidney functionality, the degree of hypertension and accompanying symptoms. A preeclampsia diagnosis is considered severe if a patient has, on two separate occasions, a systolic blood pressure above 160 mmHg or a diastolic blood pressure over 110 mmHg; thrombocytopenia with less than 100,000 per microliter; right upper quadrant (RUQ) pain or epigastric pain signaling liver issues; a high serum creatinine above 1.1 mg/dL or doubling of the serum creatinine even though no kidney disease was found originally; pulmonary edema; and lastly, accompanying de novo visual or cerebral symptoms. (4)

When it comes to gestational hypertension, it is important to mention that it should not be referred to as a "mild preeclampsia". Even though it is hypertension that first appeared during pregnancy, it is not associated with the clinical picture of preeclampsia and lacks proteinuria as a symptom completely. It can also be a remnant of maternal chronic hypertension that was diagnosed before the onset of pregnancy (5).

Regarding chronic hypertension, preeclampsia can be superimposed on it as well. Hypertension happens in about 5-15% of pregnancies (6) and can be diagnosed by looking at the patient's anamnesis and finding new-onset proteinuria of more than 0.3 grams of total urine excretion over 24 hours during pregnancy in accordance with high blood pressure levels (7).

The last type of preeclampsia is the hemolysis-elevated-liver enzymes-low-platelets (HELLP)-syndrome. In this case, the woman might, additionally to preeclampsia symptoms, complain of sudden onset of right upper quadrant pain due to hepatic inflammation and edema, nausea, visual disturbances, weight gain and generalized edema. (8) Although glucocorticoids can temporarily lighten the symptoms, the only treatment is delivery via cesarian section. HELLP-syndrome is important to recognize since its complications include acute kidney failure, cerebral bleeding, stroke, disseminated intravascular coagulation (DIC), lung edema and abruptio placentae (which not only causes maternal complications but may also lead to fetal death). (9), (10), (11)

In this thesis, all the types of preeclampsia will be included. International literature about preeclampsia from 2012 to 2022 shall be reviewed. The goal is to choose relevant articles which represented new findings in preeclampsia throughout those years and looking at the outcomes of maternal and fetal death during those years. A special focus will be laid on the maternal outcomes all over the world. In this manner, a conclusion can be drawn about whether the new findings may have improved the outcomes and, if so, what research should perhaps focus on to reduce mortality and morbidity of the disease even further.

METHODOLOGY

Medical databases such as PubMed, a search engine accessing mostly the MEDLINE database, and Google Scholar were used to find articles from 2012 to 2022. With the keyword 'preeclampsia outcomes' 8,272 search results were obtained from the years 2012 to 2022; and with the keyword 'preeclampsia' a total of 21,772 results appeared in the database in those aforementioned years at the time of research. To research additional information, the keywords 'preeclampsia microRNA' and 'preeclampsia uterine pulsatile index' as well as 'preeclampsia maternal outcomes', 'preeclampsia maternal and fetal outcomes' and 'preeclampsia sFLT-1/PlGF ratio' were used.

In total, 63 sources were selected for this thesis paper. In each year, after reading title and abstract, the most relevant articles were selected to represent new findings in preeclampsia. The Best Match search algorithm (12) was strongly relied on during the selection process of the papers for this literature review. The choice was limited by the availability of free full texts and full texts accessible via the Vilnius University Virtual Private Network (VPN) using Cisco AnyConnect Secure Mobility Client. The chosen articles serve as examples for the research progress.

Furthermore, the articles serve as a guide throughout the years to demonstrate the changes of outcomes of preeclampsia throughout the years. A graph of maternal outcomes was constructed using papers from the researched decade. This graph does not focus on women from a specific area, but rather displays three main outcomes internationally. The three outcomes selected were placental abruption, HELLP syndrome and eclampsia from one study across each year of the decade.

PATHOPHYSIOLOGY

The exact pathophysiology of preeclampsia is being researched to this day – on top of this, James M. Roberts et al. proposed in 2022 (5) to consider that different subtypes of preeclampsia vary in their pathogenesis. Some papers also make the distinction between fetal and maternal pathogenic pathways; they lead, however, to the same consequences. Abnormal placentation, inflammation, secondary endothelial dysfunction, anti-angiogenic factors as well as oxidative stress have found to be contributing to the disease and have a massive impact (5) (4).

Abnormal placentation occurs when the cytotrophoblast, which normally invades the spiral artery of the maternal myometrium and remodels them into functional vessels, is not as invasive as it should be and is left with a rather narrow artery and therefore low vascularization and subsequent ischemia. Insufficient flow can also be brought on by a maternal condition called decidual vasculopathy. Atherosclerosis in the radial arteries of the decidua impact blood flow and in turn cause ischemia. Also, unsatisfactory decidualization, the changes that are supposed to happen to the endometrium, were linked to severe preeclampsia (4). These phenomena lead to an imbalance between pro-angiogenic factors like vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) and anti-angiogenic factors, especially soluble fms-like tyrosine kinase 1 (sFLT-1). (3) The constant change between oxygenation and hypoxia causes reactive oxygen species (ROS) to form, which, in turn, promote the transcription of sFLT-1 once more (4). ROS have also been found to appear due to ischemia-reperfusion injury in the endoplasmic reticuli of the maternal decidua. This triggers PKR-like endoplasmic reticulum kinase (PERK), an up-regulator for apoptotic transcription factors and a down-regulator for PlGF. To quickly summarize the pathogenic pathways that have been researched, multiple errors, i.e. abnormal placentation, occur which bring about improper vascularization. Inflammatory processes take their course, and the patient is left with a body that attempts to increase blood flow by increasing maternal blood pressure (3).

There are additional pathways which also lead to preeclampsia: insufficient release of interleukin-10 (IL-10), enhanced angiotensin II (AT-II) sensitivity and an up-regulated sympathetic nervous system response. IL-10 helps T-cells to differentiate; an inadequate amount of this cytokine supports a pro-inflammatory state of the mother. As for AT-II sensitivity, it is speculated whether the sensitivity is enhanced because there are circulating antibodies against angiotensin I (AT-I) in the blood which are responsible for increased ROS, abnormal placentation, vasoconstriction, hypercoagulability and more. Lastly, a dysregulated sympathetic nervous system response was found in women with preeclampsia. The baroreceptor reflex sensitivity, which is controlled by mechanical receptors that sense blood pressure and then send the information to the brain to either raise or lower the pressure, is decreased in this case. Interestingly, this drop in sensitivity is a normal process of aging, which could explain why older, nulliparity mothers are more likely to develop preeclampsia (4).

RISK FACTORS

The risk factors for developing preeclampsia are prior preeclampsia of the patient or of patient's parent. There is a genetic susceptibility near the gene that encodes fms-like tyrosine kinase 1 (FLT-1), which, in soluble form, contributes to the pathogenesis of preeclampsia. Chronic hypertension established before the pregnancy, diabetes mellitus, obesity or overweight, chronic kidney disease, antiphospholipid syndrome, and a non-singleton pregnancy are worth mentioning. It is also more

probable to happen for first-time mothers with advanced age who used assisting reproductive technology. (4)

A DECADE OF RESEARCH

In 2012, Shokoufeh Savaj et al. wrote an overview of the recent innovations and enhancements in the pathophysiology and diagnosis of that time. It is said that in a healthy pregnancy, placental cytotrophoblasts invade spiral arteries and that in preeclampsia there is a problem at this stage. Also, an imbalance of angiogenic and antiangiogenic factors are a significant in development of the pathology. They report on the elevation of sFLT-1 and soluble endoglin (sEng) in preeclamptic women; both are anti-angiogenic factors. They mention risk factors such as twin pregnancies, systemic lupus erythematosus and diabetes mellitus which cause an abnormally controlled oxygen supply to the important arteries such as the ovarian artery. Higher resistance in uterine arteries due to abnormal spiral artery invasion was also known to be an issue in the pathogenesis of preeclampsia as well as auto-antibodies again angiotensin receptor II. (13)

A biomarker is defined as a naturally occurring measurable item. It does not always determine how a person feels or functions but it does hint to physiological or pathological pathways in the body. (14) It can be molecular, histologic, radiographic, or a physiologic characteristic. (15)

In 2013, a study by Julien Textoris et al. researched a wide group of biomarkers to find out which ones could be used for the diagnosis of preeclampsia and the determination of its severity. 19 preeclampsia patients and 19 normotensive patients participated. The biomarkers were chosen based on the two pathogenesis pathways that were rumored to be the culprit of preeclampsia – a vascular pathway (placental hypoxia, enhanced platelet aggregation, endothelial dysfunction) and an immunological pathway (fetal tissue as allograft brings on the disease). Molecules of coagulation such as fibrinogen, fibronectin, factor VIII activity, antithrombin, protein S and protein C were compared as well as proteins involved with angiogenesis like sEndoglin and sFLT-1, and they included cell adhesion molecule sCD146, placental growth factors (PlGF) and microparticles (blebs shed and released following activation of platelets). Interestingly, out of these biomarkers, the only one with relevance turned out to be PlGF. (16) It was significantly downregulated compared to the rest of the markers. Since none of them indicated the severity of preeclampsia, the research team performed a whole-genome microarray approach. With this, they found out two occurrences: preeclampsia patients had a wider gene heterogenicity, and a gene called VSIG4 (“V-Set And Immunoglobulin Domain Containing 4”, a protein, is encoded) was upmodulated. It is not only a phagocytic receptor but also a down regulator of T-cell proliferation and interleukin-2 production and inhibits the alternative complement pathway convertases. Dysregulation of the complement system can ultimately cause accumulation of immunological debris as well as host cell damage (16).

In the same year, P. I. Gómez-Arriaga et al. (17) conducted a study about uterine artery doppler and sFIt-1/PIGF ratio as a prognostic value. They aimed to find out how well the uterine artery pulsatile index and the soluble fms-like tyrosine kinase 1 to placental growth factor ratio (sFLT-1/PlGF ratio) predicts outcomes of mother and child in early-onset preeclampsia. Uterine artery pulsatile index is assessed with Doppler sonography and is non-invasive. (18) The measurement refers to differences between the peak systolic flow and minimum diastolic flow velocity, further divided by the mean velocity. (19)

Angiogenic factors and uterine Doppler velocimetry were studied to find out their correlation concerning both early- and late-onset preeclampsia. For the angiogenic factors they picked sFLT-1, sEndoglin, adiponectin and plasminogen activator inhibitor-1 (PAI-1).

They concluded that early-onset preeclampsia patients had a higher uterine and umbilical artery doppler value. As for correlation, uterine artery resistance and sFLT-1 directly depended on each other; as well as uterine resistance index and sEndoglin. PAI-1 and adiponectin turned out to be unrelated and comparable to the healthy control group (20).

A study performed by Amaral LM et al. on pregnant rats with reduced uterine perfusion pressure (RUPP) in 2014 where progesterone in the form of 17-alpha-hydroxyprogesterone caproate was administered on the 18th day of gestation to the animals showed that this attenuates pro-inflammatory cytokines and T-helper cells. At this point in time, it was known that 17-alpha-hydroxyprogesterone caproate (17-OHPC) is used to reduce the risk of preterm births. After administration of 17-OHPC, an improvement of availability of nitric oxide showed vasodilation and reduction of umbilical artery resistance index, intra-uterine growth restriction and more (21). The study was continued in 2017 (26).

In 2015, Ayse Kirbas et al. researched the complete blood count (CBC), beta-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A) of preeclampsia patients. They took the blood samples of every patient during the first trimester screen between 11+0 to 13+6 weeks of gestation and were therefore able to compare the values effectively. The final analysis stated that the neutrophil-to-lymphocyte ratio (NLR) can make a prediction about the severity of preeclampsia - the higher the ratio, the more severe the diagnosis. The amount of PAPP-A was specific in diagnosing preeclampsia in the first place, since it showed to be lower in women with preeclampsia. PAPP-A cleaves insulin-like growth factor-1 (IGF-1), a growth factor for cells, and also acts as a precursor to major basic protein (MBP), which takes part in the hypersensitivity reaction type I by stimulating mast cells to release histamine. (22)

In 2016, Po-Jen Cheng et al. conducted a study to further evaluate the relationship between cardiovascular health and preeclampsia. They studied cardiovascular markers in patient serum of women with an uncomplicated pregnancy versus women with preeclampsia and then further

narrowed it down to comparing early-onset and late-onset preeclampsia as well as preeclampsia with intrauterine growth restriction and no intrauterine growth restriction. The team was hoping to determine if detecting certain cardiovascular disease risk factors early in pregnancy can help assuming the risk for preeclampsia and therefore prevent complications or be prepared to deal with preeclampsia in the upcoming trimesters. A number of 2,338 women participated in the study. As a result, significant markers in this study were high-sensitivity C-reactive protein, homocysteine and fasting glucose for early-onset preeclampsia and preeclampsia with intra-uterine growth restriction; while triglycerides, VLDL-cholesterol, LDL-cholesterol, fasting insulin, and homeostatic model assessment (HOMA) of insulin resistance were more elevated in late-onset preeclampsia and preeclampsia without intra-uterine growth restriction. The conductors of the study highlighted the limits of the research themselves by naming reasons such as low number cases, not taking family history, socioeconomic status or lifestyle habits into account and only performing tests between the 11^{th} and 13^{th} week of gestation. (23) Interestingly, the measurement of cardiovascular risk factors could be included in the routine screening of a pregnant woman to assess her personal risk for preeclampsia.

A year later, in 2017, Eleni G. Elia and her team focused on the predictive value of the albumin to creatinine ratio for the outcome of women and fetuses in case of preeclampsia. Albuminuria has been shown to be a conclusive sign for glomerular damage – more so than total protein excretion. They had 717 women participate in their study. The women agreed to have their albumin to creatinine ratio measured at first presentation. It was revealed that the ratio could function as an actual independent maternal and neonatal prognostic factor for adverse outcomes (about 30% increased risk of adverse outcomes for the mother and about 10% risk of adverse outcomes for the neonate). They expanded that the ratio could be used as a prognostic factor as a routine in hospitals, but it had not been implemented at that time – hospital staff would favor 24-hour urine collection or protein to creatinine ratio. (24)

loannis Bellos' study, also conducted in 2017, showed that ceruloplasmin levels were also measured at a higher concentration for preeclamptic women, whether severe or non-severe, compared to a healthy pregnant participant. (25) This will be discussed further at a later point.

As mentioned before, the study on RUPP rats in 2014 by Amaral LM et al. was continued in 2017. At this point, 17-OHPC was still only given to pregnant women to avoid preterm birth, but there was no data proving the utilization of 17-OHPC for relieving preeclampsia symptoms. This time, instead of administering the 17-alpha-hydroxyprogesterone caproate on the 18^{th} day of gestation, they administered it on the 15^{th} day of gestation and saw even better outcomes for the animal. Contrary to 2014, they saw more improvements with fetal outcomes (26).

In 2018, a study by H. Perry et al. focused on cardiac output, systemic vascular resistance, and uterine artery pulsatile index, expanding on how in preterm hypertensive disorders of pregnancy (HDP) study participants showed less cardiac output, elevated systemic vascular resistance, and a higher uterine artery pulsatile index than the control group. Contrary to this, participants with term HDP showed the same cardiac output and uterine artery pulsatile index as the control group, but a much more elevated systemic vascular resistance. These findings support, according to the research team, that the uterine artery pulsatile index changes due to maternal cardiovascular aberrations and not because of impaired trophoblast invasion to the spiral arteries. (27)

In 2019, the relationship between micro ribonucleic acids (microRNAs) and preeclampsia was inspected further by Georgios Skalis et al. (29). MicroRNAs are small, non-coding RNA molecules that function as a post-translational gene expression regulator– influencing cell proliferation, development and death. (28) In preeclampsia and in many cancers, they seem to be expressed in a different way; either being down- or upregulated compared to a healthy patient. For example, miRNA-195, miRNA-376C, miRNA-378a-5p and miRNA-210 led to an impaired trophoblast migration and invasion. miRNA-210, miRNA-21, miRNA-22 led to impaired angiogenesis. miRNA-223, miRNA-148a and miRNA-152 caused maternal immune system dysregulation. (29)

In 2020, Maurizio Mandalà reported in his paper "Influence of Estrogens on Uterine Vascular Adaptation in Normal and Preeclamptic Pregnancies" how estrogen may not only serve as a biomarker for diagnosis of preeclampsia but also as a potential treatment in the future. Lower estrogens have been shown to appear in women with preeclampsia – this happens for example due to obesity and its high leptin levels which inhibits steroid synthesis. In addition, placental hypoxia leads to reduced expression of an enzyme which is needed for estrogen development. The less estrogen a patient has, the less spiral artery invasion happens. (30)

In 2021, a study was published in which proved the maternal blood leptin to ceramide ratio serves as a more useful marker for risk identification that the previously used sFIt-1/PIGF ratio test. The blood sera of 55 different women from 23 weeks of gestation to 31 weeks of gestation were analyzed to come to this conclusion. (31) Leptin is a hormone produced by adipocytes that suppresses appetite and increases metabolic rate. A deficiency in mice showed severe obesity (32); this may explain preeclampsia's link to obesity as a risk factors. The study by Qianyang Huang et al. proved that circulating leptin levels were more elevated in women with preeclampsia. (31) Ceramides have been shown throughout the last years of research to be vital in the prediction of negative outcomes concerning diabetes type 2 and cardiovascular health. They are lipids which have an effect on the cells of the body; such as functioning in inflammation. (33) Ceruloplasmin, a serum ferroxidase, utilizes copper to exert functions in metabolism (34) and works downstream from leptin. (31) Unlike loannis Bellos' study conducted in 2017 and mentioned before, where they showed that the

ceruloplasmin levels are were measured at a higher concentration for preeclamptic women (25), Huang's et al. published work describes ceruloplasmin levels as decreased for preeclamptic women between the fifth and 29th week of gestation. (31)

Both studies propose either serum ceruloplasmin levels or the leptin to ceruloplasmin ratio could be used as a tool in the handling of preeclampsia.

In 2022, Bjoern F. Kraemer et al. explored a marker for preeclampsia severity called platelet mitochondrial membrane potential or Mmp-Index for short. The study measured the index via flow-cytometry in a total of 70 women. 16 of them were not pregnant and used as a control group; 16 of them had diagnosed preeclampsia according to the American College of Obstetricians and Gynecologists (ACOG) guidelines; 32 of them were pregnant and healthy and six patients with just isolated gestational hypertension were later included as a separate group for the study. Investigation of this marker was performed because breakdown of mitochondrial membrane potential shows apoptosis in thrombocytes. The team and others were previously able to show the correlation between the Mmp-index and severity of preeclampsia. The lower the Mmp-index, the more severe the preeclampsia turned out to be. The study group consisting of patients with isolated gestational hypertension showed a comparable Mmp-index to the healthy control group. The findings suggest that the metabolism of the mitochondria in platelets is directly associated with disease severity of preeclampsia and could serve as a biological indicator of the inflammatory status. (35)

A DECADE OF OUTCOMES

A clinical guideline written by Juan Fernando Romero-Arauz et al. in 2012 stated that preeclampsia accounts for about 50.000 maternal deaths every year at that point in time; and that every seven minutes a woman dies due to preeclamptic complications. (36) Furthermore, in accordance with the paper of Incim Bezircioğlu et al., where they studied HELLP syndrome, clinical characters, and laboratory factors were unable to predict fetal and/or maternal outcomes. (37)

An Iranian cross-sectional study by Nankali A et al. researched a sample size of 349 women who presented to Kermanshah University of Medical Sciences from 2007 to 2009 with severe preeclampsia and summarized that about 7.7% had placental abruption, 0.3% experienced HELLP syndrome and 6.3% had eclampsia (Graph 1). (38)

Additionally, the World Health Organization published "WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia" one year before, in 2011. This guideline included 23 recommendations, with either very low, low, moderate, or high evidence quality and either weak or strong strength. Different recommendations within the guidelines were added in 2018, 2020 and 2021 and will be expanded on further. Without the added or modified content throughout the years, what remained constant since 2011 was the recommendation of using magnesium sulfate (either full-

regimen or loading dose plus transfer to high-level care facility) in the prevention and treatment of eclampsia. Early delivery of the baby with maternal severe preeclampsia at term and induction of labor with mild preeclampsia or gestational hypertension at term, as well as treatment continuation with antihypertensive drugs if the woman took them before delivery (or newly-introduced for women with postpartum hypertension) remained, too. (39)

P. I. Gómez-Arriaga et al. studied the time-to-delivery interval. Neither sFIt-1/PlGF ratio nor uterine artery doppler had any predictive value for the maternal outcome; the only useful parameter mentioned is the time of diagnosis: if it is an early-onset preeclampsia, the maternal outcomes seemed to be negatively influenced. Regarding the perinatal outcome, both uterine artery pulsatile index and sFIt-1/PlGF ratio were deemed to be useful in the prediction of an outcome, sFIt-1/PlGF ratio more so than uterine artery pulsatile index, when they're used in combination with the gestational age. According to this study, the sFIt-1/PlGF ratio demonstrated great usefulness in the prediction of time of delivery; values higher than 655 was associated with a birth within the next 48 hours. (40)

TA Jido et al. reported that in the year 2013, mortality and morbidity of both mother and child improved significantly due to new research and discovery. Fetal monitoring with Doppler was emphasized as a fetal mortality and morbidity reducer. (1)

Sarosh Rana et al. compared 46 women with a normal plasma angiogenic profile in preeclampsia with 51 women without a normal angiogenic profile in preeclampsia. The sample size was chosen by women in Beth Israel Deaconess Medical Center who presented to triage and were then chosen to be evaluated for preeclampsia. The women with normal angiogenic profile can be disregarded, since they did not show any signs of abruption, HELLP syndrome or eclampsia. (41) It highlights the severity of the angiogenic pathophysiology in preeclampsia. The women with the abnormal profiles on the other hand showed in 9.8% placental abruption, in 23.5% elevated liver function tests and low platelets (almost HELLP syndrome) and in 2.0% eclampsia (Graph 1). (41)

In 2014, preeclampsia remains a leading cause of maternal and fetal adverse outcomes. (42) Chaiworapongsa T et al. summarizes that the antiplatelet agent acetylsalicylic acid reduced the incidence of preeclampsia, pre-term birth and other serious outcomes by 10% if the medicament is taken for the prevention of preeclampsia. Antioxidants, namely vitamin E, C and the amino acid L-arginine reduced the risk of preeclampsia by a striking 63% if women who have a personal or a family history of the disease received treatment by the 24th week of gestation. (43)

Chang Shu et al. studied 166 pregnant women between July 2011 and June 2012 in the First Hospital of Jilin University and released a study about it in 2014. They compared preterm and term preeclampsia outcomes with their respective control groups. Hypertension and placental abruption occurred in 15.5%, hypertension plus elevated liver function tests and low platelets occurred in 18.3% and hypertension and eclampsia occurred in 14.1% of women with preterm preeclampsia (Graph 1).

These values were equal to zero in both control groups and distinctively lower in term preeclampsia women. (44)

In 2015, during a study that used the preeclampsia integrated estimate of risk (fullPIERS) model calculator, certain maternal and fetal outcome risks were calculated. Contrary to the fullPIERS calculator recommendations, the necessary information for calculation was obtained within 24 hours of admission of the patient, instead of 48 hours. It showed that the fullPIERS model is successful to predict possible maternal outcomes as well as easy to use. The positive likelihood ratio (LR) showed the model is effective in predicting preeclampsia with a higher specificity. In total, they had a number of 322 participants, of which 4.0% had placental abruption, 1.2% HELLP syndrome and 10.2% eclampsia (Graph 1). (45)

In 2016, B. Garcia et al. reported in their study how, on the one hand, using Doppler for uterine artery resistance was successful in the identification of affected women of early-onset preeclampsia or women with intra-uterine growth restriction. On the other hand, using it to improve the maternal or fetal outcomes failed. (46)

The same year, Nwanodi OB reported about how the usage of a checklist might be helpful for improving preeclampsia outcomes. The author developed a checklist made of four parts: first and second trimester records, second and third trimester records, term and fourth trimester records and lastly outcome measures. For the first three parts, the author divided the checklist into “signs and symptoms” and the appropriate actions plus protocols for possible situation that need immediate medical attention. The last part of the checklist is divided into maternal and perinatal outcomes. Therefore, the checklist is not only beneficial for the pregnant woman and her soon-to-be-born baby, but also for the handling of future pregnancies, since it was recorded what was done for the woman and what the outcomes were. The author calls it a “continuous quality improvement assessment”. Regarding effectiveness of checklists, Nwanodi OB reports of surgical checklists that have successfully reduced mortality. As for limitations, the length and therefore the adherence to the checklist may be seen as problematic and as an obstacle for the success of the checklist. (47) However, such a checklist may be helping new residents to provide more appropriate care to women with suspected preeclampsia.

A study about soluble fms-like tyrosine kinase to placental growth factor ratio and its relation to adverse outcomes was conducted by Kedak Baltajian MD et al. at the Beth Israel Deaconess Medical Center. They included 100 women in their study from July 2013 to October 2014. It was shown that 5.0% of women had placental abruption and 5.0% showed signs of HELLP syndrome, but no data about eclampsia was recorded (Graph1). All in all, the researchers made a connection between the plasma sFlt1/PlGF ratio and adverse outcomes; maternal as well as fetal. (48)

In 2017, Agarwal S et al. conducted a literature review on the influence of vitamin D on maternal and fetal outcomes during pregnancy. Vitamin D is known to take part in calcium and phosphorous homeostasis, its anti-inflammatory effect and regulating immunity. According to the paper, some literature was able to link better maternal outcomes to the supplementation of vitamin D, while other papers did not find a correlation between the two. In the endorsing literature, the immunoregulatory effect of vitamin D is thought to oppose placental vasoconstriction and ameliorate placental invasion, therefore preventing a part of the pathophysiology of preeclampsia. Also, its effect on the renin-angiotensin-aldosterone-system, its role as an angiogenesis regulator and atherosclerosis (cholesterol uptake by endothelial macrophages) is proposed. Essentially, vitamin D is supposed to reduce the risk factors for preeclampsia. The writers of the paper mention that other studies have not come to the same conclusions, however, some were able to confirm that when more supplements such as calcium were given to the pregnant mother, the same result was observed. As for fetal outcomes, low birth weight, for example, could not be clearly linked to vitamin D supplementation but the incidence of respiratory infections after birth could be diminished. (49)

Unfortunately, the usage of 17-OHPC on preeclampsia patients has not been studied yet and a follow-up on this study is not possible.

A cohort study from 2017 inspected the ratio of velocity peaks via an ophthalmic artery (OA) Doppler measurement and its correlation to adverse outcomes in preeclampsia. From April 2014 to September 2015 at Hospital de Clínicas de Porto Alegre in Brazil, they examined women from 23 to 40 weeks of gestation. It ended up being a study with 58 participants in total. Sadly, no data was provided about placental abruption, but 12.1% of the participants had HELLP syndrome and 36.4% showed eclampsia (Graph 1). (50)

Maya Reddy et al. conducted a cohort study at Monash Health in Australia from January 1, 2016, to July 31, 2018, about the definition of preeclampsia according to ISSHP (International Society for the Study of Hypertension in Pregnancy) 2001, ACOG 2018 and ISSHP 2018. They found that the ISSHP definition of 2001 omits milder cases of preeclampsia; however, they tend to have less adverse outcomes. With the ISSHP 2001 criteria, women experienced 1.4% of placental abruption, 0.8% HELLP syndrome and 11.9% needed $MgSO_4$ (Graph 1). (51)

As mentioned before, the World Health Organization guidelines for preeclampsia were updated in 2018. One of the recommendations added was the drug treatment in pregnant women with severe hypertension. The research team concluded that the recommendation for women to take antihypertensives in pregnancy when severe hypertension is diagnosed is strong; even though the certainty of evidence was deemed “very low”. It is listed in the recommendation as of today. (52)

The next three recommendations were also added in 2018, stating that the induction of labor should be commenced in women with severe pre-eclampsia if the fetus is unlikely to survive or gain survival

strength within the next one or two weeks. This is also a strong recommendation, nevertheless, it is based on very low certainty evidence.

However, if the fetus shows to be capable or survival before 34 weeks of gestation, it is recommended to follow the protocol of expectant management, meaning no induction or immediate delivery is advised. This is only true if the severe hypertension is controlled and its bad outcomes such as organ dysfunction of the mother or fetal distress may be monitored. Again, we have a very low certainty with this recommendation. It is a weakly recommended advice.

It is the exact same scenario for women with severe preeclampsia and a fetus capable of survival between the gestational week of 34 and 36 weeks plus six days. (53)

A last World Health Organization element added to the recommendation list is to take a calcium supplement daily (1.5 to 2.0 grams) in case of low calcium intake via the diet. It is believed to reduce the risk of preeclampsia, is a strong recommendation with moderate certainty evidence. (54)

A noteworthy point is the disregard of this belief by Dr Peter von Dadelszen. He is of the opinion that calcium supplementation may in fact mask preeclampsia since it may act as an antihypertensive agent in women. (39)

For the year of 2019, it is adequate to mention that "diastolic notching" in the ultrasound waveform of the uterine arteries was researched. Especially bilateral notching (both uterine arteries) seems to have a negative effect on pregnancy outcomes. Dominik Ratiu's et al. study looked at the uterine waveforms and possible notching between the 19th and 22nd week of gestation. If notching was present, developing complications such as preeclampsia and HELLP syndrome was more likely. (55)

In 2019, Methal A. Alrubaee et al. compared fetal and maternal outcomes of preeclampsia between primigravida and multigravida women. It was performed between September 1st 2017 to 31st of August 2018 in the Basrah Maternity & Child Hospital. All in all, 218 women were examined, 110 of which were multigravida and 108 of which were primigravida. Of the primigravida women, 7.4% had placental abruption, 0.0% showed HELLP syndrome and 20.3% showed eclampsia (Graph 1). It is of interest to mention that the multigravida women had much less incidence of eclampsia but a much higher incidence of placental abruption. (56)

Pooja Wadhwani et al. compared the outcomes of the mother and the fetus in early-onset preeclampsia and in late-onset preeclampsia. Each group had 150 women respectively, so there were 300 participants in this study. The article was published in 2020, but conducted from July 2016 to October 2017 in Chandigarh, India (Department of Obstetrics and Gynecology of the Post Graduate Institute of Medical Education and Research). Out of the 300 women, 11.6% had placental abruption, 4.0% had complete HELLP syndrome and 15.3% had eclampsia (Graph 1). To distinguish the two types, early-onset preeclampsia had more adverse outcomes than late-onset preeclampsia. (57)

In 2020, the update of drug treatment for non-severe hypertension in pregnancy was published. It did not make it into the most recent WHO guidelines, but it does state that women with non-severe hypertension should be offered the use of antihypertensives, especially methyldopa and beta-blockers. (58)

Furthermore, another paper by the WHO was published about calcium supplementation before pregnancy and deemed it reasonable under the condition of further analyses. In studies done beforehand, calcium supplementation showed little to no difference in the risk of developing hypertensive disorders in pregnancy. This was based on low-certainty evidence and therefore, they advise more testing. It did not make it into the final recommendations. (59)

In 2021, the fullPIERS model makes an appearance once again. A study from Brazil identified 208 women with preeclampsia within a one-year-period. 2.4% showed placental abruption, 6.7% HELLP syndrome and 3.8% eclampsia (Graph 1). The authors express their appreciation for the fullPIERS model and state that the model may be used to discern a favorable outcome from an adverse one. (60)

The WHO added in one strong and one weak aspect to their recommendation list in 2021; it is strongly recommended to use acetylsalicylic acid (75 mg) daily for prevention of preeclampsia development, when a high or moderate risk appears. On the other hand, it is weakly recommended to start the acetylsalicylic acid by the 20th week of gestation or immediately when antenatal care is provided. (61) In 2022, Tabassum S et al. researched outcomes of preeclampsia for women who were managed in Bahrain's tertiary care hospital. From January 2018 to December 2019, this retrospective cohort study conducted in the Bahrain Defense Hospital examined a total of 142 patients with preeclampsia. As for complications, 3.5% of women experienced placental abruption, 3.5% HELLP syndrome and 2.8% eclampsia (Graph 1). (62)

To summarize the WHO guidelines, the strong recommendations were calcium supplementation and the usage of acetylsalicylic acid 75mg for prevention of preeclampsia; treatment with anti-hypertensive drugs for women with severe hypertension during and after term; using magnesium sulfate for the prevention and treatment of eclampsia; induction of labor in women with severe preeclampsia if the fetus is not capable of successful survival or not expected to be capable within one or two weeks; and early delivery at term. The publication also includes a list of supplements not proven to have a positive effect: including the supplementation of vitamin D, C and E against the development of preeclampsia and expected complications, as well as diuretics (thiazide in particular).

DISCUSSION

Looking at Graph 1, it is undeniable that preeclampsia is a syndrome of global importance, neither the economic force nor the population of the country seems to have a significant influence on the

disease's epidemiology. Complications vary widely, and it is indiscernible to pinpoint the most common one.

Placental abruption's highest incidence occurs in Asian countries with 15.5% in China and 11.6% in India, six years apart. The third highest incidence presents in the United States of America (USA) with 9.8%. At this point, it could be speculated that placental abruption as a complication of preeclampsia is likely to happen in a more populated country. The lowest incidence of placental abruption in the aforementioned context is found in Australia in 2018 with 1.4%. The average for this complication comes to about 6.2%.

HELLP syndrome as a complication reached its maximum occurrence with 23.5% in 2013 in the USA, tightly followed by the value of the Chinese study in the following year with 18.3%. In India, the value stayed between 1.24% and 4.0% throughout the years. In Brazil, a decrease in incidence is found from 2017 to 2021. It falls from 12.1% to 6.7%. The lowest incidences can be found in Australia, Iran, and Iraq with 0.8%, 0.3% and 0.0% respectively. The average percentage of HELLP syndrome in this graph comes to 6.9%.

Eclampsia has the highest bar in the graph, with a statistically significant value of 36.4% in 2017 in Brazil. The second highest occurrence percentage is observed in Iraq in 2019 with 20.3%. The lowest was reported in 2013 in the USA with only 2.0%. The average is slightly higher than that of the other two complications with about 11.2%.

It is important to mention that the created graph roughly demonstrates an international occurrence of complication frequency around the world. For each year, different countries were selected based on a scientific data that included the complications that were specifically searched for. In the years that countries' data overlapped, a direct comparison was possible. However, the information does not correlate with the trends of the entire country, rather of a specific hospital in a specific region. The significance of the graph is suboptimal due to availability of data and should be regarded as such. It simply gives a rough glance into the international situation over a decade.

Throughout the research, it becomes evident that studies have tried to identify predictive values for the outcomes and onset of preeclampsia based on the information which has been collected about preeclampsia from 2012 to 2022.

Throughout these years, especially sFlt-1/PlGF ratio, Doppler ultrasound, medications, laboratory measurements, supplements as well as certain models and checklists have been constructed, analyzed, and arranged to predict certain outcomes of preeclampsia.

Some of the possible predicting values seem to be controversial; for example, the sFlt-1/PlGF ratio seemed to have no real predictive value for maternal outcomes in 2013 (40), but in 2016, a study did suspect a correlation between the ratio and outcomes. (48)

Important to note is that the supplementations of vitamins such as vitamin D, C and E as well as L-arginine and calcium are disputed. In 2014, L-arginine and vitamin C and E supplementation supposedly reduce the risk of preeclampsia by a striking 63% for at-risk women. (43) By 2017, no certain conclusion can be made about vitamin D. (49) As of 2022, the WHO cannot support taking vitamin D, C and E for prevention. (39) Following this unclear outcome, a focus to research the benefits of L-arginine intake could prove to be fruitful.

Researchers over the years first state in 2013 that Doppler ultrasound fetal monitoring ameliorates fetal outcomes (1), in 2016 it is said that the Doppler ultrasound may identify early onset preeclampsia but cannot reduce worse outcomes. (46)

Regarding the 2016 study by Po-Jen Cheng et al., including cardiovascular risk factors in the routine screening of mothers-to-be may help in assessing her risk for development of preeclampsia. (23) Obtaining measurements of C-reactive protein, fasting glucose, triglycerides, VLDL-cholesterol, LDL-cholesterol and fasting insulin may be analyzed rather quickly. (63)

In 2017, researchers showed elevated ceruloplasmin levels for patients with preeclampsia (25); in 2021, another study mentions lower ceruloplasmin levels – specifically for women between the fifth and 29th week of gestation. (31) With that aspect in mind, it's possible to say that further research may be needed for ceruloplasmin.

It is worth mentioning the significance of 17-OHPC-administration and its results in the rat study. (21), (26) The administration of 17-OHPC led to vasodilation and therefore reduced uterine artery resistance index. The study was continued in 2017 and showed that early administration (as early as the 15th day of gestation) led to better outcomes, especially fetal, in pregnant rats. (26) Research and subsequent administration of 17-OHPC in humans could possibly lead to decrease in preeclampsia symptoms and reduce undesired outcomes. However, a patient would have to be screened for risk factors thoroughly before the 15th day of gestation, insinuating that a suspicion of the disease would have to be established by then.

Micro-RNAs, which were researched in 2019, could be determined in a woman to further narrow down possible pathophysiologies. (29) In the same year, bilateral notching of uterine arteries in ultrasound was also linked to worse pregnancy outcomes. (55) Overall, the authors of the papers agree to a certain degree with Doppler ultrasound being helpful in identifying and therefore predicting the course of a pregnancy.

The 2020 paper on estrogen suggests that estrogen could be used as a potential treatment due to potential estrogen deficiency in preeclamptic women. Less estrogen leads to less spiral artery invasion occurrence. (30) Advantages and disadvantages of estrogen treatment during pregnancy could be studied and evaluated in the future to potentially reduce risks of mortality and morbidity.

The scientific papers agree on the usefulness of the fullPIERS model. It seems to be a successful outcome predictor for women who have preeclampsia and can be used within 24 hours, according to the study conducted in 2015. (45) Interestingly, the World Health Organization does not mention or acknowledge the usage of the fullPIERS model.

The papers also concur on the practicality of acetylsalicylic acid for the prevention of the development of preeclampsia. The WHO supports it since 2022 (61), while a study in 2014 already stated that acetylsalicylic acid is supposed to lower the incidence of preeclampsia 10% if the drug is already taken for prevention of the syndrome. (43)

Lastly, the Mmp-index researched by Bjoern F. Kraemer et al. in 2022 seems to hold some promise since it could be a strong predictor in preeclampsia severity. The platelet mitochondrial membrane potential was generally lower in women with preeclampsia, having a direct correlation to the severity of the disease (35). Using the Mmp-index as an indicator of inflammatory status could prevent further complications.

CONCLUSION

The results are relevant since they show that research has been constant, though not extensive enough throughout the last decade. Potentially predictive values and factors that research papers have disagreed upon, such as the soluble fms-like tyrosine kinase 1 to placental growth factor ratio (sFlt-1/PlGF ratio), should be researched more until a consensus can be reached. More research is needed in the field of micro ribonucleic acids (microRNAs), cardiovascular risk factors, ceruloplasmin, 17-alpha-hydroxyprogesterone caproate (17-OHPC), the platelet mitochondrial membrane potential (Mmp-index) and estrogen. It seems to be evident that there is a lot of potential for improvement in the research about preeclampsia diagnosis, treatment and reducing its risk factors. Based on the results, only a few approaches are continuously followed up upon. Currently, the official World Health Organization guidelines (39) strongly support calcium supplementation, aspirin intake and anti-hypertensive drugs (pre-, throughout, and post-pregnancy) as well as the preference of using magnesium sulfate rather than other anticonvulsants. Concerning delivery, induction is recommended at a gestational age where the fetus is not yet viable or not likely to reach the needed viability within one or two weeks. Also, delivery is recommended if severe preeclampsia presents itself at term. (39) The author of this literature review agrees with the current World Health Organization guidelines. Additionally, they support the usage of Doppler ultrasound and cardiovascular risk factors for identification of possible preeclampsia in practice next to the measurement of diagnosis criteria such as blood pressure and protein in urine. Implementing the full preeclampsia integrated estimate of risk (fullPIERS) model could potentially help with identification of possible unfavorable outcomes in a small amount of time and is therefore recommended by this review. Several promising ideas have

been brought to light during the last decade – the researcher remains hopeful that the upcoming decade will investigate the interesting propositions in more depth.

As for the maternal outcomes studied in this review, it was not possible to interpret a trend in a certain direction. It did, however, show that preeclampsia complications are an international problem which underlines the importance of continuing research on the topic of preeclampsia.

REFERENCES

1. Jido TA, Yakasai IA. Preeclampsia: A review of the evidence. Annals of African Medicine. 2013 Apr 1;12(2):75.

2. Preeclampsia | Circulation Research [Internet]. [cited 2023 Feb 5]. Available from: https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.118.313276

3. Ramos JGL, Sass N, Costa SHM. Preeclampsia. Rev Bras Ginecol Obstet. 2017 Sep;39(09):496–512.

4. Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia. Circulation Research. 2019 Mar 29;124(7):1094–112.

5. Roberts JM, Rich-Edwards JW, McElrath TF, Garmire L, Myatt L. SUBTYPES OF PREECLAMPSIA: RECOGNITION AND DETERMINING CLINICAL USEFULNESS. Hypertension. 2021 May 5;77(5):1430–41.

6. Guedes-Martins L. Superimposed Preeclampsia. Adv Exp Med Biol. 2017;956:409–17.

7. Valent AM, DeFranco EA, Allison A, Salem A, Klarquist L, Gonzales K, et al. Expectant management of mild preeclampsia versus superimposed preeclampsia up to 37 weeks. American Journal of Obstetrics and Gynecology. 2015 Apr 1;212(4):515.e1-515.e8.

8. Nichols L, Harper K, Callins K. Educational Case: Hemolysis elevated liver enzymes and low platelets (HELLP syndrome). Academic Pathology. 2022 Sep 23;9:100055.

9. Saikia K, Srivastava N, Madhurima M. ANAESTHETIC MANAGEMENT OF A POSTPARTUM PATIENT WITH SPONTANEOUS SUBDURAL HAEMATOMA DUE TO POSSIBLE HELLP SYNDROME: A CASE REPORT.

10. Otçu S, Atiç EN, Yavuz D. Investigation of FAS and IL-6 Expression in Placentas with HELLP Syndrome. Int J Morphol. 2022;40(5):1228–35.

11. Suzuki S. Placental Abruption. In: Matsuda Y, editor. Cerebral Palsy: Perspective and Clinical Relation to Perinatal Complications/Events in Japan [Internet]. Singapore: Springer Nature; 2022 [cited 2023 Feb 5]. p. 145–53. Available from: https://doi.org/10.1007/978-981-19-2217-6_16

12. Fiorini N, Canese K, Starchenko G, Kireev E, Kim W, Miller V, et al. Best Match: New relevance search for PubMed. PLoS Biol. 2018 Aug 28;16(8):e2005343.

13. Savaj S, Vaziri N. An overview of recent advances in pathogenesis and diagnosis of preeclampsia. Iran J Kidney Dis. 2012 Sep;6(5):334–8.

14. Strimbu K, Tavel JA. What are Biomarkers? Curr Opin HIV AIDS. 2010 Nov;5(6):463–6.

15. Califf RM. Biomarker definitions and their applications. Exp Biol Med (Maywood). 2018 Feb;243(3):213–21.

16. Textoris J, Ivorra D, Ben Amara A, Sabatier F, Ménard JP, Heckenroth H, et al. Evaluation of Current and New Biomarkers in Severe Preeclampsia: A Microarray Approach Reveals the VSIG4 Gene as a Potential Blood Biomarker. PLoS One. 2013 Dec 9;8(12):e82638.

17. Gómez-Arriaga PI, Herraiz I, López-Jiménez EA, Escribano D, Denk B, Galindo A. Uterine artery Doppler and sFlt-1/PlGF ratio: prognostic value in early-onset pre-eclampsia. Ultrasound in Obstetrics & Gynecology. 2014;43(5):525–32.

18. Flo K, Wilsgaard T, Acharya G. A new non-invasive method for measuring uterine vascular resistance and its relationship to uterine artery Doppler indices: a longitudinal study. Ultrasound Obstet Gynecol. 2011 May;37(5):538–42.

19. Sharma N, Srinivasan S, Srinivasan KJ, Nadhamuni K. Role of Aspirin in High Pulsatility Index of Uterine Artery: A Consort Study. J Obstet Gynaecol India. 2018 Oct;68(5):382–8.

20. Tobinaga CM, Torloni MR, Gueuvoghlanian-Silva BY, Pendeloski KPT, Akita PA, Sass N, et al. Angiogenic factors and uterine Doppler velocimetry in early- and late-onset preeclampsia. Acta Obstetricia et Gynecologica Scandinavica. 2014;93(5):469–76.

21. Amaral LM, Cornelius DC, Harmon A, Moseley J, Martin JN, LaMarca B. 17-hydroxyprogesterone caproate significantly improves clinical characteristics of preeclampsia in the reduced uterine perfusion pressure rat model. Hypertension. 2015 Jan 1;65(1):225–31.

22. Kirbas A, Ersoy AO, Daglar K, Dikici T, Biberoglu EH, Kirbas O, et al. Prediction of Preeclampsia by First Trimester Combined Test and Simple Complete Blood Count Parameters. J Clin Diagn Res. 2015 Nov;9(11):QC20–3.

23. Cheng PJ, Huang SY, Su SY, Hsiao CH, Peng HH, Duan T. Prognostic Value of Cardiovascular Disease Risk Factors Measured in the First-Trimester on the Severity of Preeclampsia. Medicine (Baltimore). 2016 Feb 8;95(5):e2653.

24. Elia EG, Robb AO, Hemming K, Price MJ, Riley RD, French-Constant A, et al. Is the first urinary albumin/creatinine ratio (ACR) in women with suspected preeclampsia a prognostic factor for maternal and neonatal adverse outcome? A retrospective cohort study. Acta Obstet Gynecol Scand. 2017 May;96(5):580–8.

25. Serum ceruloplasmin levels in preeclampsia: a meta-analysis: The Journal of Maternal-Fetal & Neonatal Medicine: Vol 31, No 17 [Internet]. [cited 2023 Feb 5]. Available from: https://www.tandfonline.com/doi/abs/10.1080/14767058.2017.1340449

26. Amaral LM, Faulkner JL, Elfarra J, Cornelius DC, Cunningham MW, Ibrahim T, et al. Continued Investigation Into 17-OHPC: Results From the Preclinical RUPP Rat Model of Preeclampsia. Hypertension. 2017 Dec 1;70(6):1250–5.

27. Perry H, Lehmann H, Mantovani E, Thilaganathan B, Khalil A. Correlation between central and uterine hemodynamics in hypertensive disorders of pregnancy. Ultrasound in Obstetrics & Gynecology. 2019;54(1):58–63.

28. Dong H, Lei J, Ding L, Wen Y, Ju H, Zhang X. MicroRNA: Function, Detection, and Bioanalysis. Chem Rev. 2013 Aug 14;113(8):6207–33.

29. Skalis G, Katsi V, Miliou A, Georgiopoulos G, Papazachou O, Vamvakou G, et al. MicroRNAs in Preeclampsia. MicroRNA. 8(1):28–35.

30. Mandalà M. Influence of Estrogens on Uterine Vascular Adaptation in Normal and Preeclamptic Pregnancies. Int J Mol Sci. 2020 Apr 8;21(7):2592.

31. Huang Q, Hao S, You J, Yao X, Li Z, Schilling J, et al. Early-pregnancy prediction of risk for pre-eclampsia using maternal blood leptin/ceramide ratio: discovery and confirmation. BMJ Open. 2021 Nov 24;11(11):e050963.

32. Amorim MR, Aung O, Mokhlesi B, Polotsky VY. Leptin-mediated neural targets in obesity hypoventilation syndrome. Sleep. 2022 Sep 1;45(9):zsac153.

33. Hilvo M, Vasile VC, Donato LJ, Hurme R, Laaksonen R. Ceramides and Ceramide Scores: Clinical Applications for Cardiometabolic Risk Stratification. Front Endocrinol (Lausanne). 2020 Sep 29;11:570628.

34. Ceruloplasmin metabolism and function - ProQuest [Internet]. [cited 2023 Feb 5]. Available from: https://www.proquest.com/openview/a48ea12853951b023aa40e28c123a37a/1?pq-origsite=gscholar&cbl=49287

35. Kraemer BF, Hennis I, Karge A, Kraemer AK, Dreyer TF, Kiechle M, et al. Platelet mitochondrial membrane depolarization reflects disease severity in patients with preeclampsia. Mol Med. 2022 May 4;28:51.

36. Romero-Arauz JF, Morales-Borrego E, García-Espinosa M, Peralta-Pedrero ML. [Clinical guideline. Preeclampsia-eclampsia]. Rev Med Inst Mex Seguro Soc. 2012;50(5):569–79.

37. Bezircioğlu I, Baloğlu A, Cetinkaya B, Pirim B. Do clinical and laboratory parameters effect maternal and fetal outcomes in pregnancies complicated with hemolysis, elevated liver enzymes, and low platelet count syndrome? J Turk Ger Gynecol Assoc. 2012;13(1):1–7.

38. Nankali A, Malek-Khosravi S, Zangeneh M, Rezaei M, Hemati Z, Kohzadi M. Maternal complications associated with severe preeclampsia. J Obstet Gynaecol India. 2013 Apr 1;63(2):112–5.

39. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia [Internet]. [cited 2023 Feb 5]. Available from: https://www.who.int/publications-detail-redirect/9789241548335

40. Gómez-Arriaga PI, Herraiz I, López-Jiménez EA, Escribano D, Denk B, Galindo A. Uterine artery Doppler and sFlt-1/PlGF ratio: prognostic value in early-onset pre-eclampsia. Ultrasound in Obstetrics & Gynecology. 2014;43(5):525–32.

41. Rana S, Schnettler WT, Powe C, Wenger J, Salahuddin S, Cerdeira AS, et al. Clinical characterization and outcomes of preeclampsia with normal angiogenic profile. Hypertens Pregnancy. 2013 May 1;32(2):189–201.

42. Chaiworapongsa T, Chaemsaithong P, Chaemsaithong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. Nat Rev Nephrol. 2014 Aug 1;10(8):466–80.

43. Pre-eclampsia part 2: prediction, prevention and management. 2014. p. 531–40.

44. Shu C, Liu Z, Cui L, Wei C, Wang S, Tang JJ, et al. Protein profiling of preeclampsia placental tissues. PLoS One. 2014 Jan 1;9(11):e112890.

45. Agrawal S, Maitra N. Prediction of Adverse Maternal Outcomes in Preeclampsia Using a Risk Prediction Model. J Obstet Gynaecol India. 2016 Oct 1;66(Suppl 1):104–11.

46. García B, Llurba E, Valle L, Gómez-Roig MD, Juan M, Pérez-Matos C, et al. Do knowledge of uterine artery resistance in the second trimester and targeted surveillance improve maternal and perinatal outcome? UTOPIA study: a randomized controlled trial. Ultrasound in Obstetrics & Gynecology. 2016;47(6):680–9.

47. Nwanodi OB. Preeclampsia-Eclampsia Adverse Outcomes Reduction: The Preeclampsia-Eclampsia Checklist. Healthcare (Basel). 2016 May 1;4(2):E26.

48. Baltajian K, Bajracharya S, Salahuddin S, Berg AH, Geahchan C, Wenger JB, et al. Sequential plasma angiogenic factors levels in women with suspected preeclampsia. American Journal of Obstetrics and Gynecology. 2016 Jul 1;215(1):89.e1-89.e10.

49. Vitamin D and its impact on maternal-fetal outcomes in pregnancy: A critical review. 2018. p. 755–69.

50. Chaves MTP, Martins-Costa S, Oppermann ML da R, Dias RP, Magno V, Peña JA, et al. Maternal ophthalmic artery Doppler ultrasonography in preeclampsia and pregnancy outcomes. Pregnancy Hypertension. 2017 Oct 1;10:242–6.

51. Reddy M, Fenn S, Rolnik DL, Mol BW, da Silva Costa F, Wallace EM, et al. The impact of the definition of preeclampsia on disease diagnosis and outcomes: a retrospective cohort study. American Journal of Obstetrics and Gynecology. 2021 Feb 1;224(2):217.e1-217.e11.

52. WHO recommendations: drug treatment for severe hypertension in pregnancy [Internet]. [cited 2023 Feb 5]. Available from: https://www.who.int/publications-detail-redirect/9789241550437

53. WHO recommendations: policy of interventionist versus expectant management of severe pre-eclampsia before term [Internet]. [cited 2023 Feb 5]. Available from: https://www.who.int/publications-detail-redirect/9789241550444

54. WHO recommendation: Calcium supplementation during pregnancy for prevention of pre-eclampsia and its complications [Internet]. [cited 2023 Feb 5]. Available from: https://www.who.int/publications-detail-redirect/9789241550451

55. RATIU D, HIDE-MOSER K, MORGENSTERN B, GOTTSCHALK I, EICHLER C, LUDWIG S, et al. Doppler Indices and Notching Assessment of Uterine Artery Between the 19th and 22nd Week of Pregnancy in the Prediction of Pregnancy Outcome. In Vivo. 2019 Nov 3;33(6):2199–204.

56. Feto-maternal outcome of preeclampsia in multigravida compared to primigravida women. MJBU. 2019 Dec 25;37(2):100–5.

57. KoreaMed Synapse [Internet]. [cited 2023 Feb 5]. Available from: https://synapse.koreamed.org/articles/1144691?viewtype=pubreader

58. WHO recommendations on drug treatment for non-severe hypertension in pregnancy [Internet]. [cited 2023 Feb 5]. Available from: https://www.who.int/publications-detail-redirect/9789240008793

59. WHO recommendation on calcium supplementation before pregnancy for the prevention of pre-eclampsia and its complications [Internet]. [cited 2023 Feb 5]. Available from: https://www.who.int/publications-detail-redirect/9789240003118

60. Paulo Siqueira Guida J, Cralcev C, Costa Santos J, Marangoni-Junior M, Sanchez MP, Laura Costa M. Validation of the fullPIERS model for prediction of adverse outcomes in preeclampsia at a referral center. Pregnancy Hypertension. 2021 Mar 1;23:112–5.

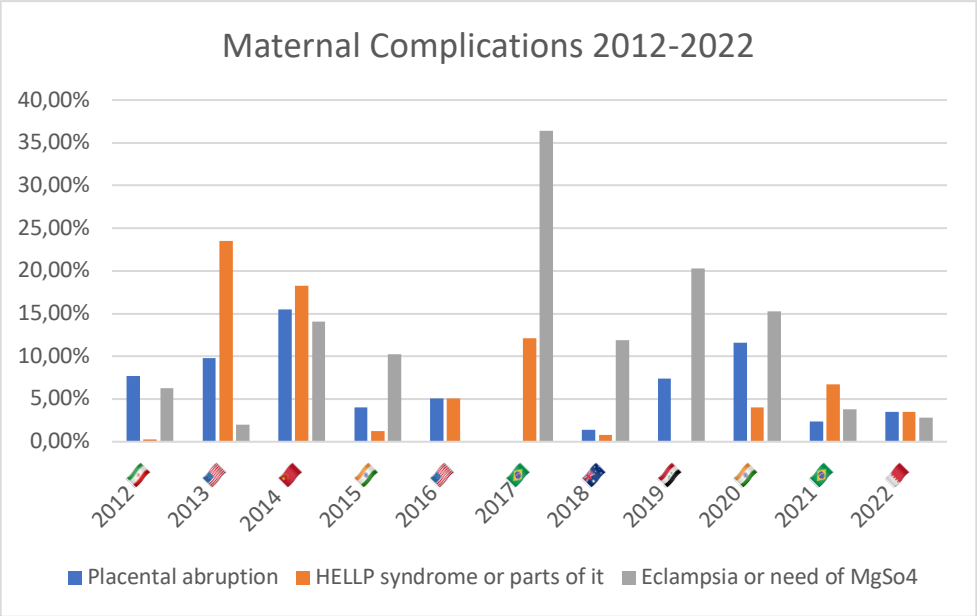
61. WHO recommendations on antiplatelet agents for the prevention of pre-eclampsia [Internet]. [cited 2023 Feb 5]. Available from: https://www.who.int/publications-detail-redirect/9789240037540

62. Tabassum S, AlSada A, Bahzad N, Sulaibeekh N, Qureshi A, Dayoub N, et al. Preeclampsia and Its Maternal and Perinatal Outcomes in Pregnant Women Managed in Bahrain's Tertiary Care Hospital. Cureus Journal of Medical Science [Internet]. 2022 May 1 [cited 2023 Feb

5];14(5). Available from: https://www.cureus.com/articles/82149-preeclampsia-and-its-maternal-and-perinatal-outcomes-in-pregnant-women-managed-in-bahrains-tertiary-care-hospital

63. Order Lab Tests and Blood Tests Online [Internet]. Testing.com. 2022 [cited 2023 Apr 7]. Available from: https://www.testing.com/

ATTACHMENTS



Graph 1: Maternal complications 2012-2022

HELLP = hemolysis, elevated liver enzymes, low platelets

MgSO4 = magnesium sulfate