Chapter

Risk Factor and Biomarker of Preeclampsia

Makmur Sitepu and Jusuf Rachmadsyah

Abstract

Preeclampsia is a multisystem progressive disorder characterized by new onset of hypertension and proteinuria or hypertension and significant end-organ dysfunction with or without proteinuria after 20 weeks of pregnancy. Recently, it has been shown that early preeclampsia is associated with abnormalities in oxygen sensing since early preeclampsia; the placenta is unable to regulate hypoxia-inducible factor 1- (HIF1-) alpha levels. The risk factors that are involved in the development of preeclampsia are also the symptoms of the metabolic syndrome and glucose metabolism disorders such as diabetes mellitus as well as insulin resistance, increased body mass index (>35 kg/m^2), and elevated diastolic blood pressure > 80 mm Hg. Further risk factors are positive family history of preeclampsia, multiple pregnancy, pregnant women over 40 years, preexisting renal disease, and clotting disorders. All biophysical and biochemical markers are shown to be used for prediction of preeclampsia. Meanwhile, it has been obvious that a single examined marker might not have the conclusion to accurately predict subsequent preeclamptic risk. Consequently, it seems to be convincing to apply history, biophysical, and several biochemical parameters to conclude the best possible detection rate.

Keywords: preeclampsia, maternal risk factors, biophysical, several biochemical parameters

1. Introduction

Preeclampsia is a multisystem progressive disorder characterized by the new onset of hypertension and proteinuria or hypertension and significant end-organ dysfunction with or without proteinuria, in the last half of pregnancy or postpartum. The genesis of the disease is laid down in early pregnancy and is characterized anatomically by abnormal remodeling of the maternal spiral arteries at the placental site.

2–The prevalence of pregnant women affected by preeclampsia (PE) [1] is 7%, commonly occurs in the second half of pregnancy and is basically identified by the existing symptoms of hypertension and proteinuria. HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count) may develop among 5–8% of these women. Preeclampsia is one of the major triggers of maternal and fetal death worldwide and a common cause of premature labor. Women with preeclamptic history are at high risk for cardiovascular diseases later in life [2]. Lowering morbidity and mortality resulting from this disease of lifestyle changes, and its preventive actions should be the main objective. The preventive treatment for those with the preeclamptic high risk has the potential to be a predictive tool also for anticipating other health disorders with serious consequences for the mothers, their offsprings, and health-care systems themselves.

2. Pathogenesis

The placenta applies a significant factor in the pathogenesis of preeclampsia because the symptoms of PE can happen in molar pregnancy, which lacks a fetus, and the disease disappears once the placenta is delivered.

Uteroplacental vascular insufficiency triggers fetus malnutrition and inadequate oxygen and nutrients. It is then identified clearly that the impact of such undernutrition condition seemingly causes coronary heart disease and hypertension in the future life [3–5]. It is easily noticed that the human placenta is only a temporary organ, but its effect on the fetus is protecting life. The correct function of the placenta necessitates the correct differentiation of the trophectoderm to set up a nutrition link between the embryo and mother [6]. In spite of numerous years of research, a holistic comprehension molecular pathogenesis of preeclampsia remains unidentified.

The present study of pathogenesis of preeclampsia carried out by Christopher Redman and Ian Sergent is assumed to happen in two-phase series of unsuitable placental condition in the first and at the beginning of the second trimester, and it badly influences the rest of the pregnancy period [7, 8]. Anatomically, placental diagnosis uncovers that the most affected part of this illness is basal plate in which the cytotrophoblast (CBT) exists [9]. In preeclamptic condition, both interstitial CTB and endovascular invasion are not deep, and consequently, it triggers impaired vascular remodeling of the spiral arteries [10]. The next phase of preeclampsia is assumed maternity-related reactions to abnormal placentation as a consequence of endothelial dysfunction and an imbalance in circulating angiogenic/vasculogenic factors such as soluble vascular endothelial growth factor receptor-1 (VEGFR-1, sFlt-1), placental growth factor (PlGF), and the changing complete growth of factor-beta receptor endoglin (CD105) [9, 11, 12] (**Figure 1**).

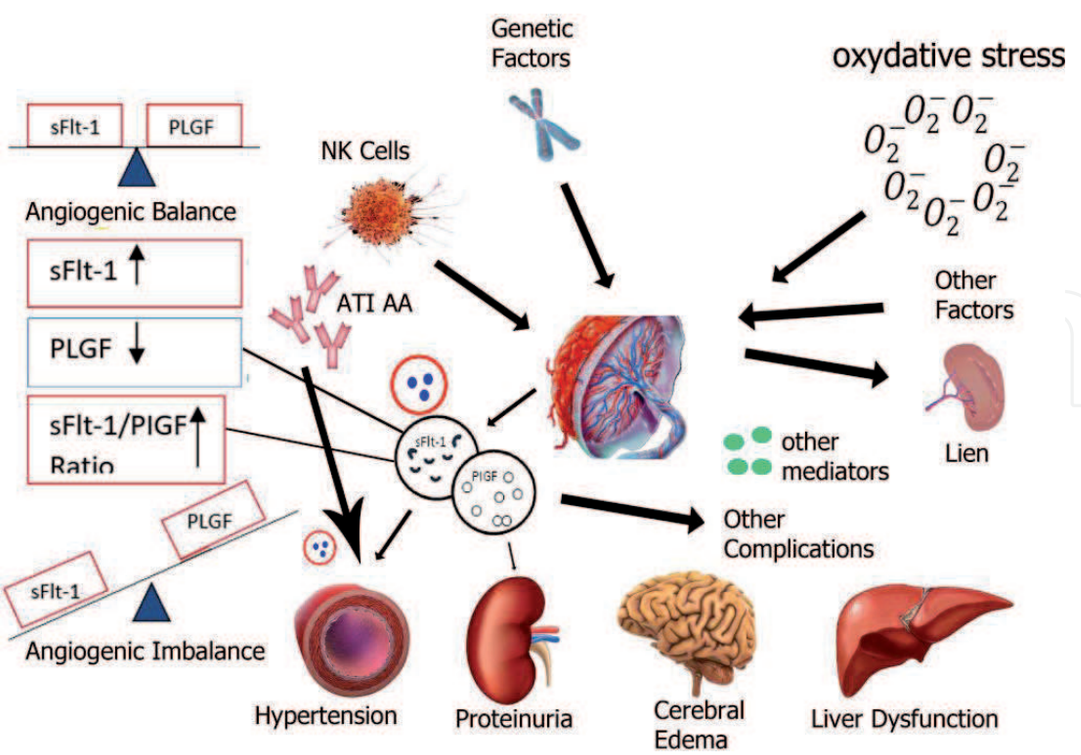

Figure 1.
In normal pregnancies, sFlt-1 and PIGF are in physiological angiogenic balance. Various factors and mediators influence the trophoblast invasion and placentation and in case of preeclampsia cause excessive production and liberation of sFlt-1 levels result in an unphysiological increase of the sFlt-1/PIGF ratio (angiogenic imbalance). Measurement of sFlt-1/PIGF ratio helps to identify women with preeclampsia and those who are likely to develop preeclampsia. ATI AA, angiotensin-converting enzyme autoantibodies. NK cells, natural killer cells.

2.1 New insights of molecule

There is substantial fact that a nonphysiological hypoxic environment subsequently in pregnancy could create such decontrol of angiogenic factors at the motherly embryonic connection. Lately, it has been indicated that the early preeclampsia is linked to anomalies regarding O_2 sensing since preliminary preeclamptic placentas failed to control hypoxia-inducible factor 1- (HIF1-) alpha levels [13]. Incessant vulnerability in nonphysiological O_2 levels in preeclampsia lowers vascular endothelial growth factor (VEGF), whereas sFlt-1 is really responsive. It is clearly accepted that produced sFlt-1 tied to VEGF and PlGF with huge similarity and consequently lowers their ability to link to their receptors [14]. The transformations act like an antiangiogenic treatment indicated in medical tests influencing similar medical symptoms such as angiogenesis dysfunction especially in vessels maturity, hypertension, proteinuria, and edema [14, 15]. Verlohren et al. [16] stated that the sFlt-1/PlGF ratio is essential to recognize females at risk for delivery and is a convincing tool to differentiate between different types of pregnancy-related hypertensive illnesses. Females are classified preeclamptic, at gestational age <34 weeks; the circulating sFlt-1/PlGF ratio predicts adverse outcomes occurring within 2 weeks [17, 18]. However, the mechanisms by which placenta-derived sFlt-1 gains access to the maternal circulation remain unclear. Rajakumar et al. [19] report that the sFlt-1 protein is highly enriched in syncytial knots which is easily detach from the syncytiotrophoblast—a finding which is increased in preeclampsia. These multinucleated aggregates are metabolically active and are capable of de novo synthesis and may thus contribute to the maternal vascular injury in PE [19].

Moreover we revealed a deregulated expression of another molecule found in the bulk of changed molecules in PE: the matricellular CCN3 protein which lead to an imbalance in proliferation and migration of human trophoblast cells and could contribute to the shallow invasion of trophoblast cells into the decidual compartment and spiral arteries observed in preeclampsia [20–23]. In addition, in our recent publication, we could show that the cholesterol transporter ABCA1 is deregulated in early-onset preeclampsia resulted from placental hypoxia [24, 25]. These results focused on the importance of the maternal-fetal cholesterol transport for adequate development of the fetus.

Microarray datasets of basal plate biopsies of both normal placentation and PE (24–36 weeks) demonstrated novel observations indicating increased expression of the leptin receptor Siglec-6 and pappalysin (PAPP-A2), a metalloproteinase that cleaves insulin-like growth factor (IGF)-binding protein-5 (IGFBP-5), in PE placentas compared to controls. Overall, these results suggest alterations in important biological processes including pathways that are regulated by leptin and IGF signals [9].

3. Early diagnosis

The aim for the early diagnosis is to start a preventive therapy by administration of 100 mg acetylsalicylic acid (ASS, aspirin) before 16 weeks of pregnancy (reduction of risk for severe preeclampsia: RR 0.1; 95% KI 0.1–0.74) [26]. It is clear that a risk calculation in the first trimester would be the most effective method to prevent preeclampsia.

Since the data on the usefulness of early administration of aspirin is still emerging, the optimal dose, which is probably 70–160 mg/d, is still under investigation. There is a known aspirin resistance in 33% of all women, which justifies the introduction of at least 100 instead of 80 mg aspirin/d. The combination of aspirin and low-molecular-weight

heparin in secondary prevention seems to bring an additional benefit over aspirin alone [27], especially for an additional hereditary thrombophilia [28].

Early detection is based on three main points which are focused on and complement each other: a detailed medical history, the collection of biophysical parameters such as blood pressure, arterial stiffness, and Doppler examination of maternal blood vessels, and the determination of biochemical parameters, which can give clues to impaired placental function.

4. Maternal risk factors

The risk factors that are involved in the development of preeclampsia are also the symptoms of the metabolic syndrome and glucose metabolism disorders such as diabetes mellitus as well as insulin resistance and assisted reproductive techniques, increased body mass index (>35 kg/m^2), and increased diastolic blood pressure > 80 mm Hg [29]. Further risk factors are positive preeclampsia of genetic background, multiple pregnancy, pregnancy above the age of 40, previous kidney-related problem, and coagulation problems [30, 31].

Specifically, prevalent coagulation problems connected with high risk of preeclampsia is factor V Leiden mutation, homozygous MTHFR mutation, hyperhomocysteinemia, existence of antiphospholipid antibodies, and the mixture of multiple thrombophilias [32].

Immune system cause-related problems can be ascribed to the high risk, for instance, in the first pregnancy. In contrast, multiparity with the same partner has lower risk [33].

As to record, 30% of women with preeclampsia are identified early with inaccurate positive rate of 5% [29]. As to the pregnancy-generated hypertension without preeclampsia, the motherly record is much more important than the maternal serum parameters and pulsatility indices of uterine arteries [34].

5. Parameters in biophysics

Mean pressure of arterial blood in the first trimester can be implemented in pairs with risk factors of maternity as a predictor of preeclampsia in the first trimester that has a detection rate of 76% for early-onset preeclampsia. Systolic blood pressure is already substantially different in the first trimester regarding the early- and late-onset preeclampsia and pregnancy-generated hypertension [35].

The arterial supply to the uterus happens normally via uterine arteries, which change into circular running arteria arcuata. In this condition, the radial artery branches and spiral arteries move deeply into the myometrium and supply the decidua and fetus during pregnancy.

Anomalous placentation and incomplete cytotrophoblast invasion typified by inadequate formation and vasodilation of the spiral arteries have long been identified as one of the main risk factors for the growth of preeclampsia [36, 37].

These morphological changes indicate abnormal uteroplacental circulation typically characterized by a persistence of the postsystolic (Notch) and high resistance indices. A prediction of the severe form of pregnancy-induced hypertension and preeclampsia is possible by examining the uteroplacental vessels in the first and second trimesters. Various publications showed that in the first-trimester screening, Doppler examination of the uterine arteries identified a certain percentage of pregnant women that later develop preeclampsia with elevated uterine resistance indices and postsystolic incisions [38–40].

About 40% of pregnant women can thus be detected at a false-positive rate of 5% [34, 41]. However, the sensitivity for the prediction of preeclampsia is significantly lower than that in the second-trimester ultrasound measurements. Higher rates of sensitivity regarding the discovery of a late-onset preeclampsia can be achieved in the second trimester of pregnancy. Several Doppler studies in the second trimester yielded detection rates of 70–80% [42, 43].

6. Biochemical parameters

The problem of the Doppler examination alone, however, lies in the low predictive value. Only in combination with biochemical markers, this evaluation is clinically relevant for a preventive therapy. In the second trimester, the combination of Doppler sonography and angiogenic factors such as PlGF/sEndoglin (sEng) and sFlt-1 is a valid prediction of preeclampsia [44].

In order to intervene preventively, high-risk population should be identified before the 16th week of pregnancy. The aim is, therefore, to predict preeclampsia at the first trimester of pregnancy.

PAPP-A was first identified as a predictive marker. PlGF is also in the first quarter of pregnancy decreased. Further promising targets for the first-trimester screening are PP-13, soluble endoglin, inhibin A, activin A, pentraxin 3, P-selectin, IGFBP-1 and IGFBP-3, adiponectin, resistin, L-arginine, asymmetric dimethylarginine (ADMA), and homoarginine. However, sFlt-1 is not suitable for screening in the first trimester [34].

6.1 PIGF (placental growth factor)

PlGF belongs to the VEGF family, is secreted by trophoblast cells, and has proangiogenic function. Preeclampsia occurs due to an impaired placentation with subsequent ischemia triggers which raised secretion of antiangiogenic factors such as soluble Fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng) in the circulation of maternity. This process creates a course of antagonizing the angiogenic factors such as PlGF [45].

PIGF was in an early focus of the research groups in the search for a suitable prediction factor. It turned out that the concentration of PlGF in a preeclamptic pregnancy did not increase to the extent as would be expected in a normal pregnancy [46, 47]. Others could show that in the first trimester, there are already significant differences between PlGF concentrations in maternal blood of pregnant women with normal pregnancy and those that develop preeclampsia during pregnancy [34, 48–50]. Since 2011, the first conventional test of the company Alere allows the quantitative detection of PIGF in anticoagulated EDTA plasma in the first trimester with fluorescence immunoassay (sensitivity and specificity 95%). The detection rate of preeclampsia using PlGF alone for the early-onset preeclampsia is between 41 and 59% and for late-onset preeclampsia 33% [51].

The latest studies show a strong connection between changed levels of PlGF and sVEGF R1 in preeclamptic pregnancy, as well as in those who will eventually develop the condition later in pregnancy. These reports are based on the findings that sVEGF R1 levels increase earlier and to a greater extent in women who eventually develop preeclampsia compared to women with normal pregnancies. In contrast, free PlGF levels in women who develop preeclampsia (compared to women with normal pregnancies) are meaningfully lower. Latest data indicate these markers to be convincing in the differential examinations of hypertensive diseases of pregnancy [52, 53].

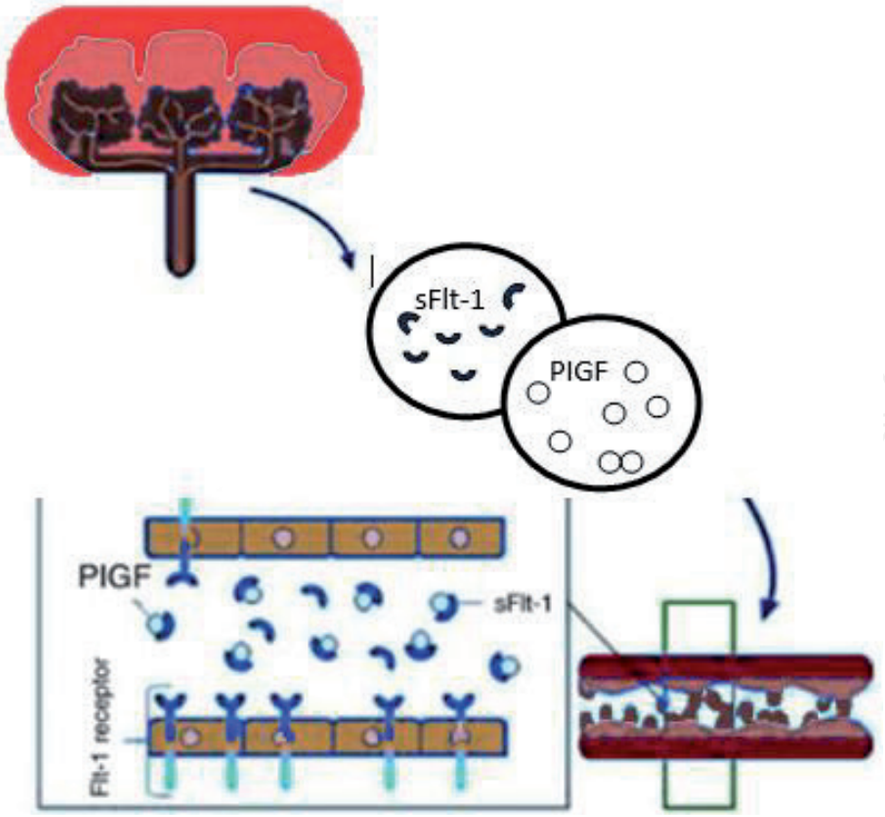

Figure 2.
An excessive production of sFlt-1 is known in patients with preeclampsia. As an antagonist, it binds with high affinity to free PIGF in maternal serum. Thereby, proangiogenic effects by binding of PIGF to membranous sFlt-1 receptors (a vascular endothelial growth factor) are inhibited and are thought to be responsible for endothelial dysfunction.

6.2 sFlt-1/PlGF ratio

Researches show that sFlt-1 is an antiangiogenic molecule and therefore seems to be involved importantly in the pathogenesis of preeclampsia. High levels of circulatings sFlt-1 in early pregnancy are associated with the later commencement of preeclampsia. An in vitro research shows that sFlt-1 inhibits tube formation of endothelial cells from human umbilical vein. In essential cytotrophoblast cell culture, sFlt-1 production and mRNA expression are related inversely to oxygen saturation. A twofold elevation in the level of sFlt-1 was also observed when normal villous explants were exposed to a hypoxic state (1% oxygen), compared with physiologic exposure to 5% oxygen. Therefore, it is reasonable that the hypoxic placenta releases an excess of sFlt-1 into the maternal circulation, which induces maternal endothelial dysfunction and clinical symptoms of preeclampsia. There is also a tendency that an excess of sFlt-1 production can trigger events in the pathogenesis of preeclampsia [55].

Especially, the sFlt-1/PlGF ratio connects to the clinical condition of the disease, differentiates between healthy and preeclamptic pregnancies, and gives a short-term prediction of disease development. Consequently, the estimation of sFlt-1 and PlGF was measured in clinical routine as a reliable and meaningful tool in examining and monitoring PE [56].

Research on antiangiogenesis factors such as sFlt-1 failed to convince as the exclusive marker for the prediction of preeclampsia in the first trimester [51]. Verlohren et al. showed that the combination of angiogenesis and antiangiogenesis factors, at least in the second and third trimesters, may offer the possibility of a risk classification by an sFlt-1/PlGF ratio. It was found that patients with preeclampsia

had a significantly increased sFlt-1/PlGF ratio compared to patients with a normal pregnancy [16, 57, 58] (**Figure 2**).

6.3 PAPP-A

Pregnancy-associated plasma protein A (PAPP-A), an insulin-like growth factor-binding protein protease, is secreted by the syncytiotrophoblast. As part of the first-trimester screening, it has long been used in risk calculation for chromosomal abnormalities. We could show that patients with decreased levels of PAPP-A in maternal blood during the first trimester develop preeclampsia [54], especially an early-onset preeclampsia as revealed also by others [34, 59, 60, 74].

6.4 Inhibin A and activin A

Both glycoprotein hormones are produced by the fetoplacental unit. Several studies exhibited that both inhibin A and activin A are increased in the first trimester in maternal blood of patients who later develop preeclampsia compared to pregnant women with normal pregnancies [60, 61]. However, no association is found between impaired trophoblast invasion and subsequent endothelial dysfunction and increased concentration of activin A [62].

6.5 PP13

The placental protein 13 plays a role in physiological placentation. Because of impaired placentation in the presence of preeclampsia, there is an increased secretion of PP13 in the first trimester of pregnancy [63–67].

6.6 PTX3

Pentraxin 3 is a secreted protein as part of an inflammatory immune response and is increased as an acute phase protein molecule [62]. Both with manifestations of PE and before clinical symptoms, there is an increased secretion of PTX 3 in the maternal circulation [60, 68–70].

6.7 P-selectin

As a cell adhesion molecule, P-selectin plays a role in endothelial dysfunction. The consequence of placental ischemia in the context of preeclampsia is endothelial dysfunction and thus increased secretion of P-selectin [71]. This is already detectable in the first trimester of pregnancy [60, 69, 70].

6.8 IGFBP-1 and IGFBP-3

Both insulin-like growth factor-binding proteins are the focus of new research. Both in early- and late-onset preeclampsia, IGFBP-1 is decreased in the first trimester. Such changes are detected by secretion of IGFBP-3 only in late-onset preeclampsia. In both cases, there is no correlation to a disturbed trophoblast invasion [72, 73].

6.9 Adiponectin

In the case of early-onset PE, adiponectin levels are higher than in the first trimester compared to normal controls. This does not apply to late-onset PE. There

is no relationship between adiponectin and PAPP-A levels and Doppler values. In addition, there is no advantage in prediction by the addition of adiponectin [75].

6.10 Resistin

Resistin levels in the first trimester are higher in patients who develop preeclampsia than controls. There is no relationship to impaired placental perfusion [75].

6.11 L-Arginine, asymmetric dimethylarginine (ADMA), and homoarginine

All three substances are part of NO metabolism. L-Arginine and L-homoarginine are increased in the first trimester at later-developing early-onset preeclampsia, as well as the ratio of ADMA/L-arginine and ADMA/L-homoarginine. This is not the case for late-onset preeclampsia and for the isolated analysis of ADMA [76].

7. Outlook

All biophysical and biochemical markers shown are used for prediction of preeclampsia. Meanwhile it has been obvious that a single diagnostic marker is not strong enough to accurately assume subsequent preeclampsia. Based on this reason, seemingly it is convincing to use historical, biophysical, and several biochemical parameters to ascertain the best possible detection rate is achieved.

Finally, one must distinguish between early- and late-onset preeclampsia in order to classify the present results correctly. The early-onset preeclampsia is defined as the onset before 34 weeks of pregnancy, the intermediate-onset preeclampsia between the 34 and 37 weeks, and the late-onset preeclampsia after 37 weeks. The late-onset PE seems to follow a different pathogenetic mechanism, since the serum parameters differ significantly as a marker of disturbed placentation in terms of predictive power [34]. The placentation disorder, according to previous published data, is a feature of early preeclampsia. The addition of biochemical markers in the first trimester is therefore particularly suitable for detection of early preeclampsia.

Poon et al. pioneered the evaluation of a few serum parameters and maternal factors in order to achieve a good predictive power of early preeclampsia. The detection rate of early-onset PE is 93.1% in the first trimester by algorithms from maternal risk factors, mean arterial blood pressure, pulsatility index of the uterine arteries, PAPP-A, and PlGF. The detection rate for the late-onset PE with an appropriate algorithm is 44.9% [34].

These named parameters can now be purchased commercially and combined with appropriate software. Akolekar et al. found that the detection rate of preeclampsia in the first trimester by a combination of several markers (PIGF, PAPP-A, PP13, inhibin A, activin A, sEndoglin, PTX3, P-selectin, blood pressure, Doppler sonography, and history) is increased significantly to a detection rate of 91% at a fixed 5% false-positive rate for early-onset PE, 79.4% for intermediate-onset PE (34–37th weeks of gestation), and 60% for late-onset PE [60]. The addition of these parameters allows a better predictive power of all forms of preeclampsia compared to the above-described relatively simple algorithm, having particular effect on a high detection rate for early-onset preeclampsia.

Further studies are expected that show which of the biochemical markers are really useful in clinical practice. The relation of costs and benefit must be explored.

Finally, the question arises that how far it may succeed in establishing the first-trimester screening tests with the consecutive possible prevention by aspirin and/or low-molecular-weight heparin, as a screening in a large, unselected collective. Since

prevention is simple and inexpensive, the obstacle is much more on a personal and cost-intensive screening tool. The investigation regarding chromosome abnormalities will depend on the basis of the consequences of abnormal test results of many factors and is always carried out only in a preselected group. Examining on preeclampsia should be for a much larger group of pregnant women, not at least because of the higher risk to get preeclampsia as a chromosomal abnormal baby and the simplicity of prophylaxis. The other essential reason for early preeclampsia risk estimation is the fact that preeclamptic pregnant women have a bigger lifetime risk for suffering heart and blood vessel disease. Better observation of this collective of patients, changing of lifestyle factors, and health education could be an important step to reduce morbidity and mortality according to cardiovascular problems worldwide.

Currently, the aspect of fetal programming is in the main focus of research. Not only the mother also the offspring bears the consequences of preeclamptic pregnancy with mostly intrauterine growth restriction like elevated risk for cardiovascular diseases and behavioral disorders, for example.

It would be desirable in the future to integrate preeclampsia risk calculation to the regular prenatal care in the first trimester. Further studies on large collectives have to determine to what extent the false-positive and false-negative findings can lead in relation to health and economic disadvantages. Even an early screening should not replace careful pregnancy monitoring.

Finally, pregnancy is not only a short time in a woman's life with the aim to deliver a baby but it is also an important time giving insights in women's health status. As we already know, pregnancy may positively influence women's health future as could be shown by studies which detected a reduced risk of developing breast cancer after pregnancy. As an indicator of risk factors, pregnancy is not only the beginning of taking care for a family but also for a better self-care [77].

8. Conclusion

To conclude, the best possible detection rate of preeclampsia seems to be convincing to apply historical, biophysical, and several biochemical parameters. A detailed medical history such as diabetes mellitus, assisted reproductive techniques, increase body mass index, family background, multiple pregnancy, pregnancy over 40 years, previous renal problem, and clotting disorder. The collection of biophysical parameters such as blood pressure, arterial stiffness, and Doppler examination of maternal blood vessels. The determination of biochemical parameter such as angiogenic factors PIGF, sFlt-1, PAPP-A, inhibin A, activin A, PP13, PTX3, P-selectin, IGFBP-1 and IGFBP-3, adiponectin, resistin, L-arginine, ADMA, and homoarginine.

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