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MicroRNA-125b as a Preeclampsia Biomarker

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ABSTRACT

Pregnancy hypertensive disorder (PHD) is a broad term referring to conditions related to disorders of high blood pressure during pregnancy. Preeclampsia is one of 4 types of PHD characterized by an increase in systolic blood pressure ≤ 140 mmHg with a diastolic pressure ≤ 90 mmHg accompanied by proteinuria of 1+ or more. Complications of PHD include peripartum cardiomyopathy, maternal mortality, pulmonary edema, cerebrovascular accident and renal failure. As consequence, early detection of PHD is crucial in preventing complications. "Preeclampsia", "microRNA-125b" and "Biomarker" were the keywords applied to scientific online databases, such as Science Direct, PubMed, and ResearchGate. A total of 46 journals were screened, reviewed and utilized with utmost precision to construct this literature review. Looking at the dangers of preeclampsia on infants and mothers, miRNA-125b has potential to be used as a biomarker of preeclampsia that can occur in the third trimester. The increase in the concentration of miRNA-125b in the first trimester causes inhibition of trophoblast invasion, which is followed by inhibition of KCNA1, GPC1, and SGPL1. All of these proteins play a role in the invasion trophoblast which is also exacerbated by the increase in the concentration of mir-125b. All in all, these symptoms and the increase of mir-125b that appear in the first trimester yield as a promising result as biomarkers of preeclampsia in the third trimester.

Key words: preeclampsia, microRNA-125b, biomarker, SGPL1, maternal, infants

INTRODUCTION

Pregnancy hypertensive disorder is a broad terminology used to refer to conditions related to high blood pressure disorders during the period of pregnancy.[1] Hypertension is the most commonly presented medical disorder observed during periods of pregnancy and complicates up to 15% of all pregnancies in women of childbearing age, which is a 25% increase in incidence in the past two decades.[2,3] Furthermore, hypertensive disorders are found to contribute to approximately 7% to 12% pregnancy-related maternal deaths.[2] The inclining incidence of pregnancy hypertensive disorder is associated with obesity, advanced maternal age and women who have associated comorbidities.[3] Moreover, women with chronic hypertension are associated with a fivefold higher risk for peripartum cardiomyopathy, maternal mortality, pulmonary edema, cerebrovascular accident and renal failure.[4–6] Furthermore, there are four classification of pregnancy hypertensive disorders namely chronic hypertension, gestational hypertension, preeclampsia and preeclampsia superimposed on chronic hypertension.[7]

Preeclampsia is a gestational disorder and multiple systems disorder related with elevation of systolic blood pressure of equal to or greater than 140 mmHg alongside with a diastolic blood pressure of equal to or greater than 90 mmHg and accompanied with a proteinuria of 1+ or more (0.3 g per 24 h).[8]

Hypertension and proteinuria during pregnancy coincides with dysfunctions of maternal organs which could be renal insufficiency.[9] Preeclampsia occurs after the 20th week of pregnancy and is estimated as one of the most common complications of pregnancy; affecting 5-10% of pregnant mothers and accounts for 40% of fetal deaths worldwide.[8,10] In Indonesia alone, preeclampsia is the third highest leading cause (13%) of maternal mortality, after bleeding (45%) and infections (15%), with an increasing trend of 40% per year and 80% inclining incidence of pre-eclampsia associated-comorbid in pregnant women.[11] It is universally acknowledged that preeclampsia started as asymptomatic, with defects in trophoblast cells invasion as well as spiral artery remodeling in the phase of early pregnancy, which ultimately affects abnormal placentation, entailing to placental ischemia and maternal systemic syndrome in the later phase of gestation.[12] Infants born to preeclamptic mothers were associated with an over fivefold increased risk for infant mortality, a three to sevenfold increased risk for poorer birth outcomes, a three to fivefold increased risk for low birth weight, and compromised neurodevelopmental index.[13]

MicroRNAs (miRNAs) are short RNA molecules consisting of 19 to 25 nucleotides in size that control post-transcriptional silencing of the targeting genes.[14] Recent studies suggest that miRNAs are shown to be upregulated in the development of preeclampsia and are suggested to inhibit angiogenesis, trophoblast cells proliferation, placentation and migration.[15] One of the highly upregulated miRNAs, miRNA-125b, could be a promising early non-invasive biomarker.[15–18] Research shows that miRNA-125b is upregulated as early as the 12^{th}-13^{th} week of gestation in the first trimester.[17] The upregulated miRNA-125b upregulated in preeclampsia is responsible for inhibited trophoblast invasion via Potassium Voltage-gated Channel Subfamily A Member 1 (KCNA1) and transfection of miRNA-125b suppresses endothelial function through Glypican 1 (GPC1).[16] Among these candidate target genes, miRNA-125b agonists is found to reduce both mRNA and protein levels of sphingosine-1-phosphate lyase 1 (SGPL1) in plates of placenta trophoblast cells, thus showing an inverse correlation with miRNA-125b expression.[17] SGPL1 is a key regulator for normal metabolism of lipids. Altered SGPL1 expression results in severe developmental and functional defects in the basal and chorionic plates of trophoblast cells causing the physiological symptoms of preeclampsia.[17] Furthermore, decreased SGPL1 is associated with congenital malfunctions in angiogenesis regulation, vascular maturation, cardiac development and immunity.[17,19] The upregulated mi-RNA-125b in the first trimester presents the clinical symptoms shown in the later trimester of pregnancy.[16]

Nowadays, women whom preeclampsia was suspected, a ratio of serum sFlt-1 to PlGF is used as predictive factor of the absence or presence of preeclampsia in the short term.[20] Unfortunately, at one week the positive predictive value was 21%, and at four weeks, it was 18%.[21] In regards to current biomarker testing, a new biomolecular approach associated with miRNA-125b is suspected to show promising results in diagnosing preeclampsia in the first trimester. As no prior literature review has discussed this before, the authors aim to discuss and evaluate microRNA-125b potential as a biomarker of preeclampsia. In this review, the authors hope to provide a new theoretical basis for the biomarker of preeclampsia.

MATERIALS AND METHODS

The review method used was by means of literature review. The literature references are of relevant journals from renowned search engines Science Direct, PubMed, and ResearchGate. Keywords such as “Preeclampsia”, “microRNA-125b” and “Biomarker” are searched on the search

engines. The criteria of inclusion were that of all biomarker for preeclampsia and association to miRNA. Preferred studies should be at least 10 years old since the year of publication and no newer studies contradict against the information provided. From 93 journals that were reviewed, 46 were found to be suitable as reference for this paper. The reviewed information evaluated and analyzed for validity, objectivity and reliability is interpreted and compiled into one scientific literature review.

RESULTS AND DISCUSSIONS

Pathophysiology of miRNA-125b in Preeclampsia

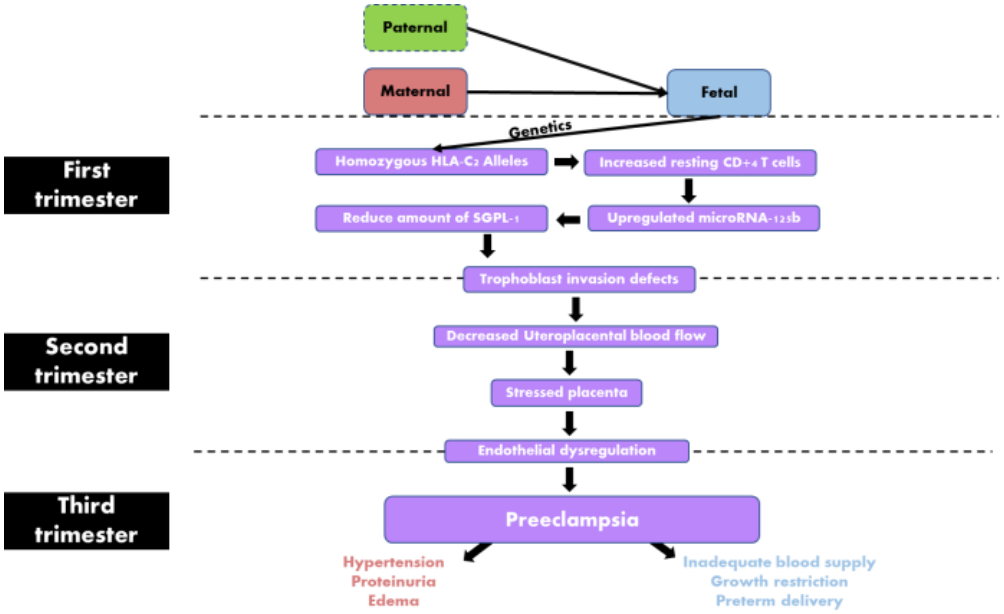

Figure 1. Pathophysiology miRNA-125b induced preeclampsia

As shown in Figure 1, a genetical pathophsiology of preeclampsia is proposed. A study in China revealed that the occurrences of preeclampsia increase only when homozygous HLA-C2 alleles appear in the fetus, indicating that preeclampsia happens when both the paternal and maternal genes carry the HLA-C2 allele.[22] It is also proposed that higher HLA-C expression results in a stronger HLA-C-restricted T-cell response.[23] As a consequence, the resting CD4+ T cells enrich expression of miRNA-28, miRNA-125b, miRNA-150, miRNA-223, and miRNA-382 in the first trimester.[17,24] One of which, miRNA-125b, is found to reduce both mRNA and protein levels of sphingosine-1-phosphate lyase 1 (SGPL1) in plates of placenta trophoblast cells causing developmental defects.[17] The failure of trophoblast uterine interactions in the first trimester leads to a stress response in the placenta which subsequently affects growth and development of the villous tree, affecting oxygen and nutrients transport to the fetus in the second trimester.[17,25]

Stressing of Syncytiotrophoblasts, cells that line the placental villi in contact with maternal blood, releases a complex mix of factors, including pro-inflammatory cytokines, exosomes, anti-angiogenic agents, and cell-free fetal DNA, into the maternal circulation.[26,27] These disrupt maternal endothelial function resulting in a systemic inflammatory response, the clinical syndrome of preeclampsia.[26] Stressed placenta leads a systemic inflammatory response resulting from disruption of the homoeostatic functions of the maternal endothelium, including regulation of clotting, fluid transfer, and blood pressure.[19,25] As consequence, higher levels

of placental apoptotic debris, placental senescence, cell-free fetal DNA, maternal serum pro inflammatory cytokines, soluble receptor (sFLT) for vascular endothelial growth factor (VEGF), and the lower levels of placental growth factor (PlGF) can be detected.[28–30] Elevated levels of sFlt are suspected to bind and reduce the bioavailability of VEGF towards the maternal endothelial cells, impairing endogenous production of nitric oxide (NO), causing vasoconstriction of blood vessels, and thus hypertension.[31] In terms of endothelium dysregulation, preeclampsia is a global systemic syndrome which can affect many organs such as kidney, liver, nervous system and the coagulation cascade presented as physiological preeclamptic symptoms detected in the third trimester of pregnancy.[9]

Role of miRNA in Preeclampsia

Preeclampsia has complex pathophysiologic mechanisms involved in the process of its pathogenesis. It is a syndrome caused by a variety of factors, mainly including abnormal placental function, immune- system alterations, increased inflammatory activation, abnormal balance of angiogenic and antiangiogenic factors, metabolic changes.[32] Placental dysfunction can result in increased release of extracellular vesicle-derived miRNAs, circulating placental factors that have been conserved to contribute to the pathogenesis of preeclampsia.[33,34] Trophoblast cells have been found to have important links to the pathogenesis of preeclampsia through FOXA1 inhibition and the trophoblast cells placental invasion blockade by highly expressed miRNA-20a.[35] In pregnancy hypertensive disorder patients, studies showed a significant increase in miRNA-1233 expression that suppresses the expression levels of HoxB3–major regulator of angiogenesis–which leads to proliferation and trophoblast cells invasion decrease in placental tissue from pregnancy hypertensive disorder patient.[35,36] Another three preeclampsia rodent model studies show elevated miR-210 in part driven by HIF-1α and NF-κBp50, induced by hypoxia and/or immune-mediated processes may contribute in preeclampsia by inhibiting anti-inflammatory Th2-cytokines.[37]

miRNA125b as Biomarker Third Trimester of Pregnancy Hypertensive Disorder

miR-125b in pregnant women can be detected from several different sites, the plasma from the mother, where it is often called the maternal circulating miR-125b and the placental cells, where it is called as placental miR-125b.[38–40] Circulating miR-125b supposedly comes from the placenta itself, as one *in vivo* study suggests, making the maternal circulating miR-125b and placental miR-125 closely related to one another.[41] Normally, the placental miR-125b will experience an eight fold change from the first to the third trimester.[39] In women who went on to develop preeclampsia (PE), one of the subtypes of the hypertensive disorders of pregnancy, several studies exhibit a significant over expression of maternal circulating miR-125b by the 12th or 13th week of pregnancy when compared to the healthy control group.[2,16,17,38] Entering the third trimester, PE symptoms have established and the level of circulating miR-125b in women that has developed symptoms of PE is significantly lower than the level of plasma miR-125b found in normal healthy women.[16,40] miR-125 levels in peripheral whole blood is also down regulated in women with clinically diagnosed PE, gestational hypertension, another subtype of hypertensive disorder of pregnancy (PHD), and intrauterine growth restriction.[40] These findings support that the progression of miR-125 in PE women and normal women were reversed and screening of PE can start as soon as entering the first trimester or around 12th week or 13th week of gestation.

miR-125b over expression in the first trimester on PE women has been discovered to directly cause the down

regulation of trophoblast cell surface antigen 2 (Trop-2) placental expression, as it is found that miR-125b targets Trop-2 expression in several tissues, including cancer and placenta.[38,42,43] Trop-2, a surface marker for trophoblasts, is also found to be down regulated in hypoxic conditions, a common condition in PE women.[38,44,45] miR-125b also directly targets the KCNA1 glycoprotein, usually found on trophoblast cells, and GPC1 on vascular endothelial cells, with higher levels of miR-125b in the first trimester is associated with a decreasing KCNA1 and GPC1.[16] As both Trop-2 and KCNA1 are found in trophoblast cells, it is concluded that miR-125b can inhibit trophoblast invasion from the first trimester, long before symptoms manifest, and may lead to the development of PE, which is characterized by hypoxic conditions in the placenta, thus further down regulate the expression of Trop2.[16,38,46] In the same study, it was also discovered that miR-125b is directly involved in tube formation in human umbilical vascular endothelial cells or HUVECs, with administration of GPC1 can reverse the effect caused by miR-125b, and this may present as a sign leading to endothelial dysfunction caused by an over expression of miR-125b in the first trimester.[16,46] The role of miR-125b in IL-8 up regulations has been observed through the interaction of SGPL-1 and miR-125b, as an up regulated level of miR-125 will decrease the number of SGPL-1 and in turn increase the level of IL-8, a commonly found inflammation cytokine in PE and thought to be one of the major factors on PE development in the first trimester.[17]

Potential miRNA-125b Inhibitor as Prevention in Third Trimester Pregnancy Hypertensive Disorder

Research by Licini et al. using a placenta sample in the first trimester (12th week gestational age) showed decreased Trop-2 expression in preeclampsia compared to normal pregnancy.[38] This was supported by overexpression of miR-125b in the first trimester and underexpression of miR-125b in the third trimester of placental PE with a significant reduction compared to placental CTR.[38–40] Besides, over expression of miR-125b in the first trimester led to inhibition of KCNA1 and GPC1 expression. The level of KCNA1 and GPC1 mRNA significantly decreased as much as ± 51% and ± 35% and as much as 30% and 50% on the decreased levels of KCNA1 and GPC1 proteins.[16] In the same study, a significant increase in miR-125b expression led to 58.6% inhibition of trophoblast invasion. Experiments using the miR-125b inhibitor significantly counteracted the inhibitory effect of miR-125b invasion. Also, inhibition of trophoblast invasion was associated with decreased KCNA1 by over expression of miR-125b.[16] The inhibitory effect of miR-125b was also inhibited by elevated GCP1. Both of these were evidenced by the addition of KCNA1 and GCP1 levels in the test sample.[16] Research that has been conducted by Yang et al. using the human trophoblast cell line, HTR8/SVneo cells, found that SGPL1 levels decreased by overexpression of miR-125b. Test with the addition of miR-125 inhibitor can increase SGPL1 levels which can improve trophoblast invasion in placenta PE.[17]

In conclusion, miRNAs that play a role in the incidence rate of preeclampsia. According to research, miRNA-125b is often causing preeclampsia by inhibiting trophoblast invasion in suppression of KCNA1, GPC1, and SGPL1. The potential of using miRNA-125b as a biomarker of preeclampsia can be maximized, considering that the pathogenesis of miRNA that causes preeclampsia varies greatly in each individual. Research to date that has been carried out in vivo strongly supports the increase in miRNA-125b concentrations as a cause of preeclampsia.

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