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Effect of Pravastatin on Lipid Profile and Pregnancy Outcome in High Risk Preeclampsia

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Abstract— Preeclampsia is the leading cause of morbidity and mortality worldwide. Etiology, and pathophysiology are poorly understood with a recent theory as two stages disorder. The main hypothesis result from a defect in remodelling of spiralis artery, while late-onset preeclampsia is generally considered as maternal factor preeclampsia. Delivery remain the main treatment option, as ACOG already recommended low dose aspirin for high risk pregnancy to reduce mortality rate. Lipid abnormalities has effect on endothelial function which is the main pathogenesis and risk factor of preeclampsia. In pregnancy, lipid metabolism changes occured for fetal growth and development. Pregnant women with preeclampsia has significantly higher lipid profile. Statin is considered safe and has advantages in treating dyslipidemia. Randomized clinical trial were done to assess effect of pravastatin in 71 high risk preeclampsia pregnant women. Clinical trial were done in two groups. Control group (Group A) take 80mg aspirin only as recommended by ACOG until 36 week of pregnancy. Intervention group (Group B) take aspirin and additional 20mg pravastatin twice daily since 18 weeks until 36 week of pregnancy. Maternal lipid profile before and after treatment on both groups were assesed. Maternal outcome and baby outcome were assessed on both groups. There is no significant difference viewed from between groups on initial test of lipid profile. Even after therapy, total cholesterol and triglyceride keep on increasing significantly ($p<0,005$ and $p<0.001$ respectively). There is also an increase of LDL but it was not significant ($p<0.114$). After therapy, there is also no significant difference can be seen between groups. However, there are tendencies of lower HDL and LDL on group B who received pravastatin rather than in group A who did not get pravastatin. At the end of pregnancy, most of the subject had hypertension mark by MAP elevation. But the result was not significant ($p<0.336$). There were no significant difference of baby outcome between two groups ($p<0.2$). Most babies birthweight is in line with gestational age according to Lubchenco curve.Additional pravastatin 20mg twice daily did not provide a significant result compared to single aspirin therapy on lipid profile as therapy to prevent preeclampsia which is currently used. Pravastatin did not improve or aggravate pregnancy outcome, neither maternal nor fetal.

Keywords— Preeclampsia, pravastatin, aspirin, lipid profile, mother outcome, fetal outcome

1.Introduction

Preeclampsia is a pregnancy specific disorder which affects multiple organ system. This disorder affects 2% - 8% of all pregnancies and is the leading caused of maternal mortality and morbidity worldwide [1]. Preeclampsia account for 50.000 to 60.000 death worldwide. Incident of preeclamsia in United States of America (USA) has increased as much as 25% in the last two decades [2]. Based on research conducted by Indonesia Ministry of Healt together with United Nations Population Fund (UNPFA) in 2012, mother mortality risk in Indonesia is 1 in 65 thousand which is considered high compared to other ASEAN country. Leading caused of mother mortality in Indonesia is hypertension induced pregnancy which is 39 in 100.000

births, and Sulawesi is a region with the highest mortality due to hypertension, which is 65 in 100.000 livebirth [3].

Etiology, pathogenesis, and pathophysiology of preeclampsia are poorly understood. Recent theory proposed that preeclampsia is a two stages disorder due to imbalance of pro-angiogenic and anti-angiogenic factors. The main hypothesis of preeclampsia result form a defect in the spiralis artery remodeling, which leads to a cellular ischemia of placenta, which in turn result in an imbalance between anti-angiogenic and pro-angiogenic factor. If the imbalance is in favor to anti-angiogenic factors, it will affect all organ system, which in turn leads to fetal growth restriction [4].

Theory of preeclampsia etiology due to placental disruption of placenta has become the main guideline in understanding the pathophysiology, diagnosis, and therapy of preeclampsia. Based on this theory, the outcome of this pathological condition should lead to fetal growth restriction. Instead, 80% of birth from preeclampsia mother are born at term, sufficient or large for gestational age. As consequence, "late onset" preeclampsia is generally considered as maternal factor preeclampsia [5].

Delivery remained the main option for preeclampsia management, as there is no effective prevention. The US Preventive Services Task Force (USPSTF) and American College of Obstetrician and Gynecologist (ACOG) has performed research and recommend the use of low dose aspirin for prevention of high risk preeclampsia women [6]. Even though there is no prevention for preeclampsia, mortality rate can be reduced. High risk preeclampsia women who did not receive therapy during pregnancy are seven times more likely to die from complicaton of preeclampsia compared to those who receive aspirin during pregnancy [7].

Research in cardiovascular field found that lipid serum has effect on endothelial function, and are one of the main causes of endothelial dysfunction [8]. Some research also shown that endothelial disfunction is associated with dyslipidemia [9]. Endothelial dysfunction is the main pathogenesis and risk factor of preeclampsia [10] and premature delivery [11].

Statin is effective in reducing morbidity and mortality of cardiovascular patient and safe for long term use [12]. On research performed by Jorge et al., statin were given for 15 days to hypercholesterol rabbit, and they found reducing in lipid peroxidase and Low Density Lipoprotein (LDL) oxidation on artery wall, therefore reducing aorta aterosclerotic and improving endothelial dysfunction which is one of pathogenesis of preeclampsia [13]. Efficacy and safety of pravastatin were conducted by Santinga et al., for 16 weeks to elderly patient gives a significant reduction of total cholesterol (21,9%), LDL (30,9%), triglyceride (16,7%), and significant enchancement of HDL (11,3%) as compared to control [14].

In pregnancy, important lipid metabolism changes occured for fetal growth and development. Lipid metabolism and concentration increase on first trimester, characterized by increased maternal adipocyte cell deposit and hypertrophy [15]. Based on cross-sectional research conducted by Sattar et al., on lipid level in normal pregnancy, they found that women with fetal growth restriction has low cholesterol level [16]. Pregnant women with preeclampsia has a significantly higher total cholesterol, LDL, trygliceride, and lower HDL [17]. Women who have cholesterol level higher than 205 mg/dL has 3,6 fold risk (95% CI 1,23-10,51) to suffer from preeclampsia, and women with triglyceride higher than 133 mg/dL has risk 4.15 fold (95% CI 1,5-11,49) higher to suffer from preeclampsia [10].

The underlying pathogenesis of preeclampsia on hyperlipidemia is generally caused by body fat accumulation on pregnancy due to hyperphagia and increased of lipogenesis. Fetal demands for free fatty

acid (FFA) increases as gestation proceeds. Lipoprotein lipase (LPL) produced by syncytiotrophoblast and cytotrophoblast represents one potential mechanism for increasing placental lipid transport. LPL activity increase 3 fold in term [18]. FFA in circulation is a main contributor to preeclampsia and mediate endothelial dysfunction through some mechanism, insulin resistency, production of nitrite oxide, oxidative stress, proinflammation cytokine, renin-angiotensin system activation, and endothel cell apoptosis [19].

Currently, statin is still categorized as "X" drugs by Food and Drug Administration (FDA), based on studies on animal and human which shown fetal abnormalities due to the use of this drug, therefore the use of these drugs on pregnant women must consider its advantages and disadvantages. Observational studies conducted by [20] in British Medical Journal (BMJ) showed that the use of statin in first trimester of pregnancy is associated with the risk of congenital malformation. The risk of congenital malformation is as high as 6,3%, but after elimination of diabetes as comorbid, malformation risk become insignificant [20].

Out of the other seven type of statin, pravastatin is hydrophilic and found in minimal amount in embryo [21]. Even though risk of malformation and adverse effect on pravastatin use on pregnancy become insignificant, studies and recommendation on dyslipidemia treatment in pregnancy is limited because pregnant women are more often excluded in clinical trial [22].Studies on the use of pravastatin by Medical Genetics has be reported to FDA and they found no genetic malformation or abnormal outcome [23]. Many other studies in Canada and Europe gave similar result. Therefore, giving statins is expected to provide prevention to preeclampsia [13].Statin and aspirin clinical benefits has been reviewed through meta analysis studies and it was found that pravastatin dan aspirin combination treatment gives more benefits compared to single therapy [24].

Birthweight reflect intrauterine growth and it is an important indicator in perinatal morbidity and mortality. Lubchenco published weight and length graphic in percentiles to assess birthweight and birthlength. This assessment is widely used and important in newborn baby management and nutrition plan [25].

Because of the high morbidity and mortality rate of preeclampsia and the prospect of new treatment in prevention of preeclampsia, it is interesting to know the effect of pravastatin to maternal lipid profile, maternal outcome, and baby outcome in high risk preeclampsia pregnancy.

2. Methods

This study is a part of a multicenter randomized controlled trial named INOVASIA (Indonesia Pravastatin to Prevent Preeclampsia Study, clinical trial gov identifier: NCT03648970). Randomized clinical trial were done to 71 pregnant women within 10-19 weeks of pregnancy, with live and no congenital anomaly fetus, who met inclusion criterias. The criterias were history of preeclampsia on previous pregnancy; have at least two of main clinical risk factor (age >40 years old, obesity, history of preeclampsia in the family, history of polycystic ovary syndrome, nulliparity, interval of 10 years or more since a previous pregnancy, multiple pregnancy, chronic hypertension, chronic renal disease, preexisting diabetes, assisted reproductive technology, family history of cardiovascular disease, and low social economy status), abnormal uterine artery doppler at 18 – 20 weeks of pregnancy, MAP >90 mmHg, blood pressure > 130/85 mmHg. Any subject who did not comply was excluded.

Clinical trial were done in two groups. Control group (Group A) take 80mg aspirin once daily from second trimester until 36 week of pregnancy. Intervention group (Group B) take 80mg aspirin once daily and additional 20mg pravastatin twice daily since 18 weeks of pregnancy until 36 week of pregnancy. Maternal lipid profile before and after treatment on both groups were assesed. Maternal outcome and baby outcome

were assessed on both groups.

3. Result

Table 1. Demographic characteristic of subject and homogeneity test on both groups

Variable	**Aspirin** (n = 28)	**Aspirin + Pravastatin**(n = 29)	**Total**	**p-value**
Age (years)	34.0 ± 6.2	33.6 ± 4.6	33.8 ± 5.4	0.777
≤ 35	16 (57.1)	19 (65.5)	35 (61.4)	
> 35	12 (42.9)	10 (34.5)	22 (38.6)	0.516
BMI (kg/m^2)	27.3 ± 5.3	28.7 ± 6.9	28.0 ± 6.1	0.383
Underweight [a]	1 (3.6)	2 (6.9)	3 (5.3)	
Normal	7 (25.0)	6 (20.7)	13 (22.8)	
Overweight	11 (39.3)	8 (27.6)	19 (33.3)	
Obese	9 (32.1)	13 (44.8)	22 (38.6)	0.661
Parity[b]	1 (1-2)	2 (1-2)	2 (1-2)	0.705
0	1 (3.6)	4 (13.8)	5 (8.8)	
1-3	24 (85.7)	25 (86.2)	49 (86.0)	
≥4	3 (10.7)	0 (0.0)	3 (5.3)	0.123[c]
MAP Initial (mmHg)	93.9 ± 13.8	94.7 ± 11.3	94.3 ± 12.5	0.815
60-90	13 (46.4)	12 (41.4)	25 (43.9)	
>90	15 (53.6)	17 (58.6)	32 (56.1)	0.701
MAP highest ANC	98.2 ± 15.3	101.8 ± 15.5	100.1 ± 15.4	0.378

All value in n (%) and mean ± SD, except stated otherwise. Comparison between groups were analyzed using independent t-test for continued variable (numeric) and Pearson Chi-square test for categorial variable.

[a]Underweight were assessed as BMI <18,4 kg/m^2; Normal if BMI = 18,5-24,9 kg/m^2; overweight if BMI = 25-29,9 kg/m^2; and obese if IMT >30 kg/m^2.

[b]Value stated in median (Q1-Q3). Differences between groups were analyzed using Mann-Whitney U test

[c]Comparison between groups were analyzed using Fisher's Exact test

BMI : Body Mass Index; MAP : Mean Arterial Pressure; ANC : ante-natal care

Samples taken on this studies is 71 subject. Of this 71 subject, 36 subject were on group A and 35 subject were on group B. Fourteen subject were later drop out. From the table above, most subject were 35 years old or less on both groups. Mean age on both groups does not differ. Mean BMI is overweight. Both groups mean parity were 1-3 parities. Mean MAP on both groups are 94 mmHg. Highest MAP during pregnancy increased around 5 – 7 mmHg on both groups.

Table 2. Comparison of risk factor and previous disease history on intervention and control group

Variable[a]	Aspirin (n = 28)	Aspirin + Pravastatin (n = 29)	Total	p-value
Chronic Hypertension	7 (25.0)	7 (24.1)	14 (24.6)	0.940
Gestational Hypertension	2 (7.1)	2 (6.9)	4 (7.0)	1.000
Preeclampsia	10 (35.7)	14 (48.3)	24 (42.1)	0.337
Eclampsia	2 (7.1)	6 (20.7)	8 (14.0)	0.253
Autoimmune Disease	1 (3.6)	0 (0.0)	1 (1.8)	0.491

[a]Previous disease history before pregnancy

Value in n (%). Comparison analysis using Pearson Chi-Square or Fisher's Exact Test

Table 3. Comparison of lipid profile between intervention and control group before and after therapy

Variable		Aspirin (n = 28)	Aspirin + Pravastatin (n = 29)	Total	p-value (Pre-Post)	p-value (inter-group)
Total Cholesterol (mg/dL)	Pre	253.2 ± 55.3	232.7 ± 51.6	242.8 ± 53.9	**0.005***	0.091
	Post	288.6 ± 78.5	267.2 ± 73.0	277.7 ± 75.8		
LDL (mg/dL)	Pre	169.4 ± 51.5	153.2 ± 48.6	161.2 ± 50.3	0.114	0.071
	Post	191.2 ± 65.1	164.6 ± 55.8	177.7 ± 61.5		
HDL (mg/dL)	Pre	44.1 ± 6.3	44.7 ± 6.9	44.4 ± 6.5	0.117	0.656
	Post	47.2 ± 6.8	45.5 ± 6.3	46.4 ± 6.6		
Triglyceride(mg/dL)	Pre	195.9 ± 101.7	175.9 ± 71.1	185.9 ± 87.5	**<0.001***	0.686
	Post	276.9 ± 134.7	315.5 ± 163.0	296.6 ± 149.7		

Value in mean ± SD. Comparison between groups and pre-post analysis using two-way ANOVA test
LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

*p<0.05.

Initial profil lipid test on each subject were done after sample randomize and subject were given therapy based on their groups. Retest on lipid profile were done on 36 week gestational age to see changes after therapy.Lipid profile tended to increase on both groups in the third trimester. Significant changes could be noticed on total cholesterol and triglyceride level.

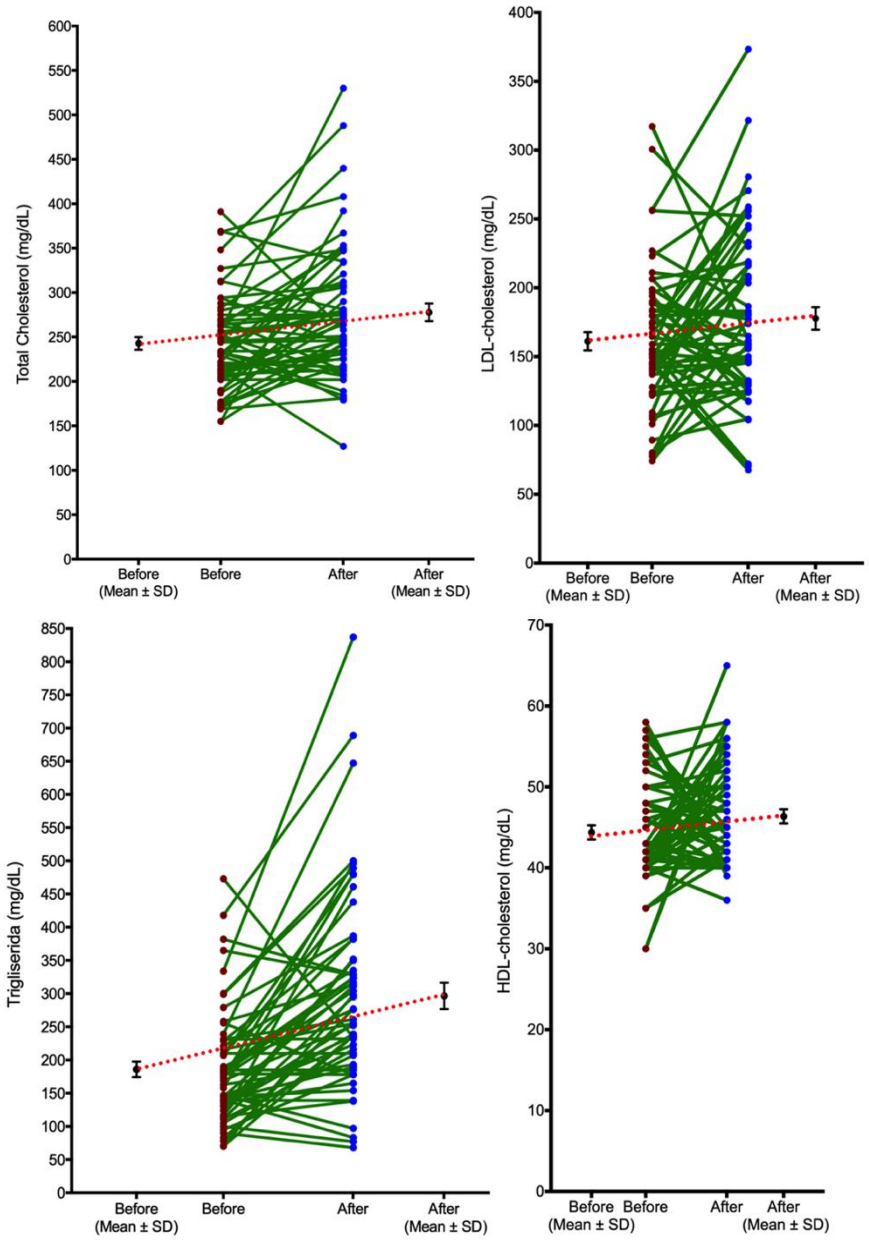

Figure 1. Comparison of lipid profile before and after therapy on all samples (n=57)

There is no significant difference viewed from between groups on initial test of lipid profile. Even after therapy, total cholesterol and triglyceride kept on increasing significantly ($p<0,005$ and $p<0.001$ respectively). There was also an increase of LDL but it was not significant ($p<0.114$). After therapy, there was also no significant difference could be seen between groups. However, there were tendencies of lower HDL and LDL on group B who received pravastatin than in group A who did not get pravastatin.

Table 4. Comparison of maternal outcome and baby outcome on control and intervention group

Variable	Aspirin (n = 28)	Aspirin + Pravastatin (n = 29)	Total	p-value
Maternal Outcome				
Normal	14 (50.0)	11 (37.9)	25 (43.9)	
Hypertension	2 (7.1)	4 (13.8)	6 (10.5)	0.336
Preeclampsia	5 (17.9)	2 (6.9)	7 (12.3)	
Severe Preeclampsia	7 (25.0)	12 (41.4)	19 (33.3)	
MAP on delivery (mmHg)	109.2 ± 18.3	110.1 ± 17.6	109.2 ± 17.8	0.852
MAP 48 hour after delivery (mmHg)	98.6 ± 17.0	103.1 ± 15.6	100.9 ± 16.3	0.300
Baby Outcome				
Birthweight (gram)	2829.8 ± 915.5	2795.5 ± 781.1	2812.4 ± 842.3	0.879
SGA	1 (3.6)	4 (13.8)	5 (8.8)	
AGA	25 (89.3)	25 (86.2)	50 (87.7)	0.200
LGA	2 (7.1)	0 (0.0)	2 (3.5)	

Value in n (%) and mean ± SD. Comparison between groups were analyzed using independent t-test for continue variable (numeric) and Fisher's Exact test for categorial variable.
MAP: *Mean Arterial Pressure*; SGA: Small for Gestational Age; AGA: Appropriate for Gestational Age; LGA: Large for Gestational Age
*p<0.05.

At the end of pregnancy, most of the subject had hypertension mark by MAP elevation. But the result was not significant (p<0.336). Only about 37% subject on group B were normal. At delivery, there were no MAP difference on both groups, which was around 110mmHg. Both groups MAP decreased 48 hours after delivery, but the value was not significant. There were no significant difference of baby outcome between two groups (p<0.2). Most babies birthweight were in line with gestational age according to Lubchenco curve. Even though there were few pregnancies have to be terminated early, due to maternal or fetal indication, birthweight was still in line with gestational age. There were no congenital abnormalities found on all samples.

4. Discussion

Most of samples on this studies who has high risk of preeclampsia were in age group of under 35 years old. Even though Cunningham classify pregnancy over 35 years as a risky pregnancy, however, most population of Makassar residents has pregnancy at younger age [26-27]. Based USA demographic data, there was up to 30% increase risk of preeclampsia for woman who has pregnancy over 34 years old. Duckitt (2005) conducted a sistematic reviewed and concluded that women over 40 years old has nearly two fold risk to suffer from preeclampsia, on both nullipara (RR 1,68; 95%CI, 1,23-2,29) and multipara (RR 1,96, 95%CI, 1.34-2.87) [28].

Mean BMI on both sample laid in overweight category on initial measurement. Overweight pregnant women in Makassar has grown worrisome. Pregnant patients with BMI above normal are more common to be found. Looking from economic growth in the past 5 years, Makassar has experienced acceleration up to 8,03% [27], therefore purchasing power increased and lifestyle changes. Excessive BMI is associated with insulin resistency, which is a risk factor to the development of preeclampsia [29].

Pregnancy induced hypertension are more often found in nulliparous than multiparous women and increasing in line as the age reach over 35 years old. According to systematic review conducted by Bartsch (2016), risk of preeclampsia rise two fold in nulliparous women [30]. Study conducted by Morikawa (2013) in Asian women in Japan, the risk of hypertension in nulliparous women are 1,3 fold [31]. Other studies explained that nulliparous and preeclampsia is caused by imbalance of sFlt-1 angiogenic factor [32]. In this study, it was found that parity distribution in both group laid in median 1 to 2 parities, which is not in the high risk group.

Various health care center in other country has started using MAP value to asses hypertension risk factor. Meta-analysis conducted by Cnossen et al., showed that MAP might be able to become predictor for preeclampsia better than sistole and diastole measurement [33]. MAP cutoff value for normal pregnant women is 90 mmHg [34]. The best time to do MAP screening for preeclampsia is on 11 to 13 week and 20 to 24 week of gestational age [35]. In line with BMI, initial MAP mean on both groups were above normal. High MAP could means that blood vessel cannot compensate to hemodynamic increase due to pregnancy. Symphatetic nerve activation, intra-abdominal and intravascular fat, and natrium retention may lead to increased renal reabsorbtion, and renin-angiotensin system, which is thought to be the main cause of hypertension pathogenesis due to excess body weight [36].

Lipid profile on both groups before intervention has exceed reference value compare to non-pregnant women. This is because the test was done when pregnancy was already in the second trimester. Since the end of first trimester, lipid metabolism is generally in anabolic phase. There is a surge of lipid synthesis and fat deposit to fulfill fetal energy requirement on third trimester [34,36].

During the third trimester, lipid physiology transition to a catabolic phase and reduced of insulin sensitivity (increased of insulin resistance). Reduced of insulin sensitivity leads to lypolisis of triglyceride deposit in adipocyte cell. The increase of human placental lactogen (HPL) hormone on third trimester also stimulate the lipolysis. Insulin resistance result in decrease of lipoprotein lipase (LPL) on adipocyte cell and causes reduced of fatty acid uptake from triglyceride-rich plasma [36]. This result in an increase of triglyceride disproportion up to 2-4 times before third trimester of pregnancy [38]. This study is also shown that there was a significant surge of total cholesterol and triglyceride after therapy on both groups. Total cholesterol value were obtained from summation of various cholesterol component [TC = LDL + HDL + (TG:5)] in accordance to changes in triglyceride[39].

Additional pravastatin on group B also shown the same result. There were a surge of total cholesterol, LDL, and triglyceride on third trimester. Compared to group A, elevation of LDL level on group B was more controlled. This is in accordance to pravastatin mechanism of action, which is to reduce blood cholestrol through increasing LDL receptor (LDLr). Increase amount of LDL receptor will enchance catabolism of all lipoprotein containing apo-B, including triglyceride. Triglyceride is contained in every lipoprotein in various amount, one of them is LDL. Increasing LDL catabolism due to statin will also reduce triglyceride levels in the blood. Statin ability to reduce triglyceride is an additional effect of the drug. In the study conducted by Branchi et al (1999) on atorvastatin, simvastatin, fluvastatin, and pravastatin, showed that the ability of

statin to reduced triglycerida was only half of statin in lowering LDL[40]. In line with Pan HY (1990) study on pravastatin monotherapy (5mg, 10mg, 20mg), total cholesterol decreased 17%-24%, LDL decreased 23%-35%, HDL increased 8%-9%, while triglyceride decreased was only 6%-9% [41].

On the study conducted by Santinga et al (1994), 20mg of pravastatin were given to primary hypercholesterolemia elderly for 16 weeks provides significant improvement lipid profile, with no significant adverse effect, even after the therapy continued for 96 weeks. However, there was exclusion of sample with type I, III, IV familial hypercholesterolemia, type V hyperproteinmeia, endocrine, renal, hepatic, metabolic, cardiovascular disease, and consumption of corticosteroid, tiazid, diuretic, beta adrenergic blocker, and women who took conjugated estrogen therapy [14]. The duration of pravastatin given in this study was between 16 to 18 weeks. Duration of pravastatin given was supposedly enough to give effect to lipid profile. Interestingly, triglyceride tended to increase on group B rather than group A. Primary data showed that 2 subjects from group B were outliers (Figure 1). First subject was a 36 years old woman on her fourth pregnancy, BMI 31,57 (obese), initial MAP 90mmHg and history of persistent preeclampsia on her previous pregnancy that needed anti hypertension therapy. On initial test, triglyceride level was 334 mg/dL and on second test, triglyceride level became 837 mg/dL. Pregnancy was terminated preterm due to hypertension, 180/110 mmHg, and baby outcome 2100 gram appropriate to gestational age. Second subject was 41 years old woman, also on her fourth pregnancy, BMI 25,48 (overweight), initial MAP 83,3 mmHg, and history of previous preeclampsia. Initial test showed that triglyceride level was 239 mg/dL. At the end of pregnancy, triglyceride levels became 647 mg/dL. Pregnancy ended at term, birthweight 3900 gram appropriate to gestational age. Prominent hypertriglyceridemia may be caused by pancreatitis in pregnant women and usually occur in women with familial chylomicronemia syndrome, other genetic disorder to triglyceride metabolism or other disorder which may increase triglyceride plasma such as diabetes. The incidence of hypertriglyceride can be exacerbated by physiologic changes in pregnancy [37,42]. However, there were no further investigation performed on both subjects. Hypertriglyceride is the result of disruption in LPL activity. LPL is an enzyme that responsible to hydrolisis of triglyceride in chylomicron and VLDL. People with impaired LPL activity, both primary or secondary, have high fasting triglyceride serum. Insulin resintence results in excessive VLDL production and disrupt LPL and lipolysis activity. Secondary causes of lipolysis disruption are obesity, insulin resistance, and type 2 diabetes mellitus. Primary causes of lipolysis are familial chylomicronemia syndrome, APOA5 (apolipoprotein A5) deficiency, GPIHBP1 (glycophosphatidylinositol-anchored high-density lipoprotein-binding protein 1), and famillial hypertriglyceridemia. Based on laboratory report, patient blood sample showed the formation of supernatant chylomicron cream floating on the serum, which is a sign of familial chylomicronemia syndrome [43].

Based on guideline published by American Heart Association (AHA) 2013, the use of statin to reduce blood cholesterol on high risk cardiovascular patient, are defined based on therapy intensity and mean LDL expectation after therapy. Therapy intensity is differentiated by high, medium, and low intensity. On high intensity statin therapy, LDL level is expected to decrease $\geq$50%, moderate intensity statin around 30%-50%, and low intensity statin $\leq$30%. Pravastatin 20mg twice daily is classified as moderate intensity. Lipid profile on pregnant women rise in linear as the gestational age, therefore moderate intensity pravastatin has not been able to reduce lipid profile of pregnant women, which is still on a rise in line with gestational age. To optimize statin therapy, studies on other statin intensity (dosage and other statin regiment) to the extent that it did not cause adverse effect could be futher explored [44].

Pravastatin therapy shows similar resultwith aspirin only therapy on pregnancy hypertension outcome and newborn outcome based on Lubchenco chart. Preeclampsia and MAP enhancement at the end of pregnancy

could still be found in both groups. Majority of fetal outcome was in appropriate gestational age based on Lubchenco chart, which mean that preeclampsia occur on late-onset and did not affect uteroplacenter circulation. In this study, lipid profile was not differed significantly by pravastatin therapy, as it is well known that lipid is required for fetal growth. Sattar (1999) found that pregnancy with intrauterine growth retardation tends to occur in pregnant women with low cholesterol level [16].

There were no congenital abnormalities found on the use of pravastatin, consistent with study performed by Constantine (2016) [23]. This study was also consistent with early studies of pregnant women exposed to statin and fibrate carried out by some researchers such as Bateman (2015) [20], Ofori (2007) [45] and Winterfield (2013) [46]. Therefore, there is still opportunity for studies in the use of pravastatin on earlier gestational age or customized dose to achieve better maternal outcome. There were 14 drop out subjects, 8 from group A and 6 from group B. The reason was headache, dyspepsia, noncompliance, migration, and infection. There was 1 subject suffered from tuberculosis on second trimester. Intrauterine growth retardation was found, but she was excluded because tuberculosis itself could lead to intrauterine growth retardation.

5. Strength and Weakness

Research on the use of statin in pregnant women was not widely conducted for safety reason. Early studies generally done as observational, case control, cross sectional, and cohort. Most studies were done on case report of intentional or unintentional use of statin or fibrate on first trimester to see its teratogenic effect. Further research was carried out by Constantine (2016) in controlled randomized double blind by giving pravastatin to 10 pregnant women with a promising result [45]. In this studies, we carried out a randomized clinical trial study with larger sample than Constantine while considering its safety use to pregnant women by choosing a relatively safe statin drug, at a relatively safe time, on second trimester, in a sufficient period of therapy, as well as assessing maternal and fetal outcome. Subject on this study showed a good homogenity. This study compared lipid profile changes and maternal and fetal outcome between groups (aspirin and aspirin+pravastatin).

The drawback of this research was the amount of drop out subjects therefore it affected statistic outcome. There were subjects that showed outliers lipid profile value which may be due to abnormalities not included in exclusion criteria which also affectedthe statistic result. Blood test performed in this study were done randomly as subjects walk-in to clinic and comply inclusion criteria and did not do 8 hours fasting before blood test for lipid profile. There were also no control on diet for subjects in this study.

6. Conclusion

Additional pravastatin 20mg twice daily did not provide a significant result compared to single aspirin therapy on lipid profile as therapy to prevent preeclampsia which is currently used. Pravastatin did not improve or aggravate pregnancy outcome, neither maternal nor fetal.

7. References

[1] Jeyabalan A. Epidemiology of preeclampsia: impact of obesity. Nutrition reviews. 2013; 71: S18-S25.

[2] Roberts JM, Druzin M, August PA. 2013. *Classification of Hypertensive Disorders in Hypertension in Pregnancy,* Washington, The American College of Obstetrician and

Gynecologists.

[3] Tejayanti T, Harimat, Sabatini K. 2012. Disparity of access & quality : Review of maternal mortality in five region in Indonesia. *In:* KEMENKESRI (ed.). Jakarta: Ministry of Health Republic of Indonesia

[4] Gathiram P, Moodley J. Pre-eclampsia: its pathogenesis and pathophysiolgy. Cardiovascular journal of Africa. 2016; 27(2): 71.

[5] Thilaganathan B. Pre-eclampsia and the cardiovascular–placental axis. Ultrasound in Obstetrics & Gynecology. 2018; 51(6): 714-717.

[6] LeFevre ML. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: US Preventive Services Task Force recommendation statement. Annals of internal medicine. 2014; 161(11): 819-826.

[7] Mackay AP, Berg CJ, Atrash HK. Pregnancy-related mortality from preeclampsia and eclampsia. Obstet Gynecol. 2001; 97(4)**:** 533-538.

[8] Sima AV, Stancu CS, Simionescu M.Vascular endothelium in atherosclerosis. Cell and tissue research. 2009; 335(1): 191.

[9] Kalar MU, Kalar N, Mansoor F, Malik AR, Lessley T, Kreimer S, Bilal M. Preeclampsia and Lipid levels–a case control study. International Journal of Collaborative Research on Internal Medicine & Public Health. 2012; 4(10).

[10] Enquobahrie DA, Williams MA, Butler CL, Frederick IO, Miller RS, Luthy DA. Maternal plasma lipid concentrations in early pregnancy and risk of preeclampsia. American journal of hypertension. 2004; 17(7): 574-581.

[11] Jiang S, Jiang J, XU H. Maternal dyslipiidemia during pregnancy may increase the risk of preterm birth : a meta-analysis. Taiwanese Journal of Obstetrics and Gynecology. 2017; 56(1)**:** 9-15.

[12] Kusters DM, Lahsinoui HH, Van De Post JA, Wiegman A, Wijburg FA, Kastelein JJ, Hutten BA. Statin use during pregnancy: a systematic review and meta-analysis. Expert review of cardiovascular therapy. 2012; 10(3): 363-378.

[13] Jorge PAR, Almeida EAD, Ozaki MR, Jorge M, Carneiro A. Effects of atorvastatin, fluvastatin, pravastatin, and simvastatin on endothelial function, lipid peroxidation, and aortic atherosclerosis in hypercholesterolemic rabbits. Arquivos Brasileiros de Cardiologia. 2005; 84(4)**:** 1-6.

[14] SantingaJT, Rosman HS, Rubenfire M. Efficacy and safety of pravastatin in the long term treatment of elderly patients with hypercholesterolemia.The American journal of medicine. 1994;96 (6)**:** 509-515.

[15] Herrera E. Lipid metabolism in pregnancy and its consequences in the fetus and newborn. Endocrine. 2002; 19(1): 43-55.

[16] Sattar N, Greer IA, Galloway PJ. Lipid and lipoprotein concentrations in pregnancies complicated by intrauterine growth restriction. The Journal of Clinical Endocrinology & Metabolism. 1999; 84(1): 128-130

[17] Gohil JT, Patel PK, Gupta P. Estimation of lipid profile in subjects of preeclampsia. The journal of Obstetrics and Gynecology of India. 2011; 61(4): 399.

[18] Magnusson-Olsson AL, Hamark B, Ericsson A, Wennergren M, Jansson T, Powell TL. Gestational and hormonal regulation of human placental lipoprotein lipase. Journal of lipid research. 2006; 47(11): 2551-2561.

[19] Ghosh A, Gao L., Thakur A, Siu PM, Lai CW. Role of free fatty acids in endothelial dysfunction. Journal of biomedical science. 2017; 24(1): 1-15.

[20] Bateman BT, Hernandez-Diaz S, Fischer MA, Seely EW, Ecker JL, Franklin JM, Huybrechts KF. Statins and congenital malformations: cohort study. BMJ. 2015;350: h1035.

[21] Edison RJ, Muenke M. Mechanistic and epidemiologic considerations in the evaluation of adverse

birth outcomes following gestational exposure to statins. American Journal of Medical Genetics Part A. 2004;131(3): 287-298.

[22] Barrett HL, Nitert MD, McIntyre HD, Callaway LK. Normalizing metabolism in diabetic pregnancy: is it time to target lipids?. Diabetes care. 2014;37(5): 1484-1493.

[23] Constantine MM, CLEARY K.Pravastatin for the prevention of preeclampsia in high-risk pregnant women. Obstet Gynecol. 2013;121 (201)**:** 1-7.

[24] Hennekens CH, Hollar D, Agatston AS. Aspirin and statins to decrease risks of cardiovascular disease–the need for wider utilization. US Cardiology. 2004; 1: 43-44.

[25] Kiserud T, Benachi A, Hecher K, Perez RG, Carvalho J, Piaggio G, Platt LD. The World Health Organization fetal growth charts: concept, findings, interpretation, and application. American journal of obstetrics and gynecology. 2018; 218(2): S619-S629.

[26] Cunningham FG, Leveno KJ, Bloom SL. 2014. Preconceptional counseling in Williams Obstetrics. New York, McGraw-Hill Education.

[27] DINKESMAKASSAR 2018. Profil Dinas Kesehatan Kota Makassar. PemKot Makassar.

[28] Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *Bmj*. 2005; 330(7491): 565.

[29] Lopez-Jaramillo P, Barajas J, Rueda-Quijano SM, Lopez-Lopez C, Felix C. Obesity and preeclampsia: common pathophysiological mechanisms. Frontiers in Physiology, 2018; 9: 1838.

[30] Bartsch E, Medcalf KE, Park AL, Ray JG. High Risk of Pre-eclampsia Identification Group. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ. 2016;353: i1753.

[31] Morikawa M, Yamada T, Yamada T, Sato S, Cho K, Minakami H. Effects of nulliparity, maternal age, and pre-pregnancy body mass index on the development of gestational hypertension and preeclampsia. Hypertension Research in Pregnancy. 2013; 1(2): 75-80.

[32] Bdolah Y, Elchalal U, Natanson-Yaron S, Yechiam H, Bdolah-Abram T, Greenfield C, Yagel S. Relationship between nulliparity and preeclampsia may be explained by altered circulating soluble fms-like tyrosine kinase 1. Hypertension in pregnancy. 2014;33(2): 250-259.

[33] Walsh CA. Mean arterial pressure and prediction of pre-eclampsia. BMJ. 2008; 336 (7653)**:** 1079-1080.

[34] Cunningham F, Leveno K, Bloom S, Spong CY, Dashe J. 2014. Maternal physiology in Williams obstetrics. 24e,New Yoek, Mcgraw-Hill.

[35] Gallo D, Poon LC, Fernandez M, Wright D, Nicolaides KH. Prediction of preeclampsia by mean arterial pressure at 11-13 and 20-24 weeks' gestation. Fetal diagnosis and therapy. 2014; 36(1); 28-37.

[36] Jiang SZ, LU W, Zong XF. Obesity and hypertension. Exp Ther Med. 2016; 12(4)**:** 2395-2399.

[37] Grimes SB, Wild R. 2018. Effect of pregnancy on lipid metabolism and lipoprotein levels. In *Endotext [Internet]*. MDText. com, Inc..

[38] Hadden DR, McLaughlin C. 2009. Normal and abnormal maternal metabolism during pregnancy. In Seminars in Fetal and Neonatal Medicine, 14(2): 66-71, WB Saunders.

[39] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972; 18 (6)**:** 499-592.

[40] Branchi A, Fiorenza AM, Rovellini A, Torri A, Muzio F, Macor S, Sommariva D. Lowering effects of four different statins on serum triglyceride level. European journal of clinical pharmacology. 1999;55(7): 499-502.

[41] Pan HY, DeVault AR, Swites BJ, Whigan D, Ivashkiv E, Willard DA, Brescia D. Pharmacokinetics and pharmacodynamics of pravastatin alone and with cholestyramine in

hypercholesterolemia. Clinical Pharmacology & Therapeutics, 1990; 48(2): 201-207.

[42] Brahm A, Hegele RA.Hypertriglyceridemia. Nutrients. 2013;5(3): 981-1001.

[43] Rader DJ, Hobbs HH. 2017. *Disorders of lipoprotein metabolism in Harrison's Endocrinology,* New York, McGraw-Hill Education.

[44] Stone NJ, Robinson JG, Lichtenstein AH, Merz CB, Blum CB, Eckel RH, McBride P. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. Circulation. 2014; 129(25): S1-S45.

[45] Ofori B, Rey E, Berard A. Risk of congenital anomalies in pregnant users of statin drugs. British journal of clinical pharmacology. 2007; 64 (4)**:** 469-509.

[46] Winterfeld U, Panchaud A, Merlob P, Rothuizen L, Cuppers-Maarschalkerweerd B, Vial T, ... & Berlin M. Pregnancy outcome following maternal exposure to statins: a multicenter prospective study. In 2011 Joint Annual Meeting of the German, Swiss, and Austrian Societies for Clinical Pharmacology and Toxicology. 2011:72.