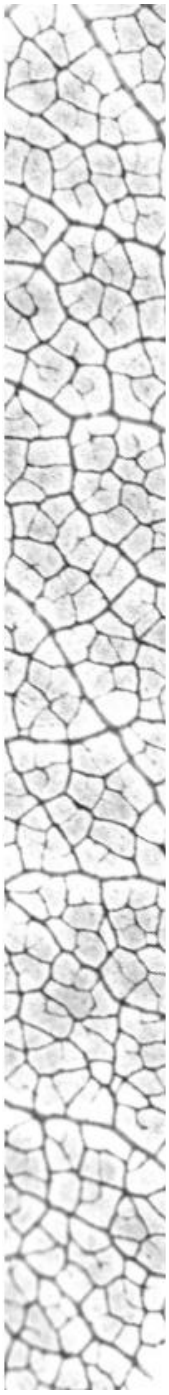

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Association of third trimester body mass index and pregnancy weight gain in obese pregnant women to umbilical artery atherosclerotic markers and fetal outcomes

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Abstract

Background: Obesity in pregnancy is a chronic inflammatory condition that can damage the cardiovascular system. This study aimed to demonstrate the correlation of third trimester body mass index (BMI) and pregnancy weight gain in obese pregnant women to the expression of umbilical artery atherosclerotic markers and fetal outcomes.
Methods: The study was conducted on obese and non-obese pregnant women in third trimester of pregnancy. An examination of atherosclerosis markers was conducted on fetal umbilical artery by immunohistochemistry technique using VCAM-1 and CD68 antibody. Fetal outcomes were examined as the measurement of infant birth weight and Apgar score of 1 minute and 5 minutes.
Results: There was strong correlation between third trimester BMI to VCAM-1 antibody expression ($r = 0.903$; $p < 0.001$) and CD68 expression ($r = 0.839$; $p < 0.001$) in umbilical artery cell. There were weak correlation and moderate correlation between weight gain during pregnancy with the expression of umbilical artery atherosclerosis markers VCAM-1 and CD68 antibody, respecetively ($r = 0.324$, $p < 0.001$; $r = 0.470$, $p < 0.001$; respectively). However, there was no correlation between third trimester BMI and pregnancy weight gain with neonatal birth weight and Apgar scores ($p > 0.05$).
Conclusion: Third trimester BMI and weight gain in obese pregnant women affect the expression of atherosclerosis markers of VCAM-1 and CD68 antibody in umbilical artery cell.

Keywords: third trimester BMI, weight gain, atherosclerosis, VCAM-1, CD68

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INTRODUCTION

Risks of obesity during pregnancy include high blood pressure abnormalities, gestational diabetes, preeclampsia, and thromboembolic complications as a risk of cardiovascular disease and often cause maternal pain and death (Aprilia et al. 2018, Bhattacharya et al. 2007, Lumbanraja 2013). Babies born to obese mothers have a tendency to have a large body weight during pregnancy and have a higher risk of experiencing intra-uterine death, congenital anomalies, and shoulder dystocia during labor. If these complications occur, delivery assistance by adequate health workers in adequate health facilities is needed so that they can be treated immediately (Handriani et al. 2015). However, if medical care is delayed, including delays in identifying pregnancy risks and dangerous signals, accessibility to health facilities, and getting good health services, it is possible for maternal death (Syarifuddin et al. 2019). Obese mothers also have the risk of passing on the tendency of obesity in their offspring and develop into metabolic syndromes such as cardiovascular disorders in childhood and adolescence where this cycle will repeat in later generations (Boney et al. 2005, Hasan et al. 2019, Megawati et al. 2017, Penfold et al. 2015). On the other hand, a pregnancy that starts with obesity also has an effect on pregnancy and fetal outcomes. Until

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now it is not known for certain whether obesity before pregnancy or during pregnancy has a negative impact on maternal and fetal outcomes (Mamun et al. 2011).

Visits of pregnant women with obesity at Dr. Soetomo Hospital, Surabaya also increase. In 2013 the number of deliveries of pregnant women in the delivery room with accompanying diagnoses of obesity was 57 cases or 2.7% of total deliveries. In 2014 the number of deliveries with obese pregnant women increased to 174 cases or 9.8% of the total deliveries with the most frequent complications of preeclampsia and caesarean section (E.V. Pesennikova et al., 2019).

The Barker Fetal Origins of Adult Disease Hypothesis (FOADH) Theory with the concept of developmental programming explains that the fetal development environment during the uterus influences disease development in adulthood. As in pregnancy with obesity, exposure to an environment of over nutrition and inflammation since early life can lead to the development of the disease in adulthood (Barker 2004, Leddy et al. 2008). There has been a lot of scientific evidence that shows an indirect relationship between obesity in mothers in relation to cardiovascular abnormalities in children and the incidence of childhood obesity. One of them is The Bogalusa Heart Study which obtained the results that obesity is the biggest contributing factor in right cardiovascular disorders even from the age of 5-8 years (Tulane Center for Cardiovascular Health 2005). However, the mechanism that shows a process of intra-uterine fetal metabolic disorders of obese pregnancy is still rarely studied.

Several studies abroad prove the occurrence of fetal aortic artery damage and umbilical artery on the umbilical cord of the fetus which is marked by the process of thickening of the artery intima as a form of early arterial damage in infants with smoking mothers, hypercholesterolemia mothers, and IUGR babies (Cosmi et al. 2010, Mecchia et al. 2009, Napoli et al. 1997, Visentin et al. 2013). The approach through examination of the umbilical artery can explain the early damage to blood vessels in the fetal cardiovascular system. This study aims to determine the relationship between BMI trimester III and weight gain during pregnancy in obese pregnant women with fetal umbilical artery atherosclerosis and fetal outcomes.

METHODS

This was a retrospective cohort study. This research was conducted in the Maternity and Pregnancy Clinic, Dr. Soetomo Hospital, Universitas Airlangga Hospital, and Soewandi Hospital, Surabaya, Indonesia from April 2016 to July 2016. The subjects of this study were third trimester pregnant women with obese BMI and third trimester pregnant women with normal BMI in the Maternity Clinic of Dr. Soetomo Hospital, Universitas Airlangga Hospital, and Soewandi Hospital. The study subjects were then divided into three study groups based on third trimester BMI and weight gain during pregnancy. The first group was the group of pregnant women with first trimester BMI and third trimester normal BMI as negative control. The second group is the group of pregnant women with normal trimester I BMI and in trimester III increased BMI to obese BMI. Whereas, the third group was the group of pregnant women with BMI in the first and third trimesters of obesity who experienced weight gain during pregnancy (Jafarzadeh et al 2018).

The inclusion criteria in this study were pregnant women with third trimester BMI and obesity during first trimester normal, pregnant women with third trimester obesity and BMI during first trimester obesity, and pregnant women with third trimester BMI and normal first trimester BMI with a weight record and height in the first trimester in the pregnancy check book. Exclusion criteria of this study were pregnant women who had a history of chronic hypertension, preeclampsia, pregestational DM, chronic kidney disease, chronic infectious diseases, multiple pregnancy, and smoking mothers. In this study, to meet ethical eligibility, prior to the study, approval from the ethics commission for basic/clinical research at Dr. Soetomo Hospital/Faculty of Medicine, Universitas Airlangga, Surabaya has been obtained.

In the fetal umbilical artery, immunohistochemical examination of atherosclerosis VCAM-1 and CD68 antibodies was performed. Fetal outcomes were examined by looking at the birth weight of the baby and the Apgar score of 1 minute and 5 minutes. Data characteristics of research subjects were analyzed descriptively. Statistical analysis was performed to see the relationship of BMI and weight gain on cell expression to VCAM-1, and CD68 antibodies in the umbilical artery were examined for normality test. The statistical test used parametric One-Way Anova for normally distributed data. If the data distribution was not normal, a Kruskal Wallis non-parametric test was conducted. The difference in outcomes in each study was analyzed using the One-Way Anova statistical test. The statistical assessment of relationship strength was expressed as r (rho) using the Pearson Moment correlation test.

RESULTS

The data presented in **Table 1** shows that the majority of research subjects belong to the age group of 20-34 years, amounting to 72.2%. The youngest subject was 18 years old, and the oldest was 41 years old. The gestational age in the third trimester when the patient delivered and the study sample was taken was mostly in the age of 38 weeks to 42 weeks (70%). Most parity status was multiparous patients. Of the weight gain of the study subjects during pregnancy, the proportion between the numbers of subjects with weight gain was

Table 1. Frequency Distribution of Research Subject Characteristics

Variables	Total (n=36)	Group I (n=12)	Group II (n=12)	Group III (n=12)
Age (years)				
<20	1 (2.8)	0	0	1 (2.8)
20-34	26 (72.2)	9 (75)	8 (66.7)	26 (72.2)
≥35	9 (25.0)	3 (25)	4 (33.3)	9 (25.0)
Gestational age (weeks)				
34-37	11 (30.5)	4 (33.3)	5 (41.7)	2 (16.7)
38-42	25 (69.5)	8 (66.7)	7 (58.3)	10 (83.3)
Parity Status				
Primiparaous	10 (27.8)	3 (25)	3 (25)	1 (8.3)
Multiparaous	26 (72.2)	9 (75)	9 (75)	11 (91.6)
Education Level				
Elementary school	4 (11)	1 (8.3)	2 (16.7)	1 (8.3)
Junior high school	6 (16.7)	0	1 (8.3)	5 (41.67)
Senior high school	24 (66.7)	10 (83.4)	8 (66.7)	6 (16.7)
Bachelor	2 (5.6)	1 (8.3)	1 (8.3)	0
Occupational Status				
Working	7 (19.4)	3 (25)	3(25)	1(8.3)
Not working	29 (80.6)	9 (75)	9(75)	11(91.6)
Weight Gain				
Proportional	18(50)	12(100)	0	6(50)
Excessive	18(50)	0	12(100)	6(50)
Labor Method				
Abdominal	19(52.8)	7(58.3)	6(50)	6(50)
Vaginal	17(47.2)	5(41.7)	6(50)	6(50)
Gestational DM				
Yes	6 (16.7)	2 (16.7)	0	4 (33.3)
No	30 (83.3)	10 (83.3)	12(100)	8 (66.7)

Group I: Group of mothers with normal trimester I BMI and normal trimester III BMI
Group II: Group of mothers with normal trimester I BMI and obese trimester III BMI
Group III: Group of mothers with obese trimesters I and III BMI

Table 2. Characteristics of fetal outcome

Variables	Total	Group I (n=12)	Group II (n=12)	Group III (n=12)
Birth weight (gr)				
≤ 2500	6 (13.8)	2 (16.7)	3 (25)	1 (8.3)
2500-3999	28 (80.6)	10 (83.3)	9 (75)	9 (75)
≥4000	2 (5.6)	0	0	2 (16.7)
APGAR score in the first 1 minute				
1-3	1 (2.7)	0	1 (8.3)	0
4-6	2 (5.6)	0	1 (8.3)	1 (8.3)
7-9	33 (91.7)	12 (100)	10 (83.4)	11 (91.7)
APGAR score in 5 minutes				
1-3	1 (2.7)	0	1 (8.3)	0
4-6	0	0	0	0
7-9	35 (97.3)	12 (100)	11 (91.7)	12 (100)

Group I: Group of mothers with normal trimester I BMI and normal trimester III BMI
Group II: Group of mothers with normal trimester I BMI and obese trimester III BMI
Group III: Group of mothers with obese trimester I and trimester III BMI

Table 3. Differences in Mean VCAM-1 and CD68 Expressions between study groups

Groups	N	VCAM-1 expression Mean±SD (cell/mm^2)	CD68 expression Mean±SD (cell/mm^2)	P-value
Group I	12	0.37±0.13^a	0.41±0.22^a	<0.001
Group II	12	1.05±0.32^b	1.33±0.33^b	
Group III	12	1.79±0.31^c	1.84±0.3^c	

The difference in letters a, b, c shows a significant difference (p <0.05) based on the LSD double comparison test.
Group I: Group of mothers with normal trimester I BMI and normal trimester III BMI
Group II: Group of mothers with normal trimester I BMI and obese trimester III BMI
Group III: Group of mothers with obese trimester I and trimester III BMI
SD: Standard Deviation; p value >0.05 indicating data are normally distributed

balanced, i.e., 18 subjects (50%) with "excessive" weight gain and 18 subjects (50%) with "proportional" weight gain according to the IOM recommendations.

Table 2 shows data on the characteristics of fetal outcomes. The distribution of the proportion for the largest infant birth weight (80.65%) was at the birth weight of 2500-3999 grams. Judging from the APGAR outcome data, infants in this study were 91.7% with a good Apgar score (7-9) in the first 1 minute the baby is born. Whereas, Apgar score at 5 minutes showed 97.3% with Apgar good score (7-9).

Table 3 shows the examination of the density of umbilical artery cell expression against immunohistochemical staining of VCAM-1 antibodies and CD68 antibodies, the highest mean cell expression in group III. The difference in expression between the three groups was statistically significant with a p value <0.001. **Table 4** shows the results of comparative test of

Table 4. Difference in Mean Birth Weight of Infants in Each Group

Variables	Group I (n=12)	Group II (n=12)	Group III (n=12)	p
Baby Birth Weight (grams)	2987±544.7	2858±667.0	3204±642.6	0.397*
APGAR score in minute 1	7 (7-8)	7 (1-8)	8 (6-8)	0.06**
APGAR score in minute 5	8.5(8-9)	8(3-9)	9(7-9)	0.03***

Data are presented with Mean ± SD and Median (min-max)
* One Way Anova test; ** Kruskall Wallis Non-Parametric test; *** Kruskall Wallis Test
Mann-Whitney Post Hoc Test: I vs II p = 0.034; I vs III p = 0.59; II vs III p = 0.019

Table 5. Statistical test results

Variables		VCAM-1	CD68	Birth Weight	AS 1 minute	AS 5 minutes
Trimester III BMI	r	0.903	0. 839	0.071	-.069	-.091
	p	<0.001	<0.001	0.340	0.344	0.298
Weight gain	r	0.324	0.470	0.068	-.239	-.278
	p	0.027	<0.002	0.346	0.080	0.051

Note: r correlation coefficient; significant correlation (p <0.05) based on the Pearson correlation test; AS: APGAR Score

fetal outcomes in 3 groups. Newborn weight (p = 0.397) and APGAR score at the first minute (p = 0.06) were not statistically significant. Whereas, the Apgar score of the 5th minute showed a significant difference in the three groups (p = 0.03). The results of Post Hoc analysis with Mann Whitney Post Hoc test found significant differences in Apgar scores in groups I vs II and groups II vs III.

Table 5 shows a statistical test of the relationship between trimester III BMI and weight gain on VCAM-1 and CD68 expression. There was a significant relationship between trimester III BMI with VCAM-1 cell expression (r = 0.903, p <0.001) and CD68 (r = 0.839, p <0.001) and weight gain during pregnancy with VCAM-1 cell expression (r = 0.324, p <0.001) and CD68 cell expression (r = 0.470, p <0.001). However, trimester III BMI was not related to birth weight outcomes for babies, APGAR scores of 1 minute and 5 minutes (p = 0.340, p = 0.344, p = 0.298, respectively). Likewise, maternal weight gain did not reveal a statistically significant relationship in infant birth weight outcomes, APGAR score of 1 minute and 5 minutes (p = 0.346, p = 0.080, p = 0.051, respectively).

DISCUSSION

The results of this study indicated an association between trimester III BMI and weight gain during pregnancy to atherosclerotic markers in the form of VCAM-1 and CD68 cell expression. The influence of trimester III BMI is greater to result in the formation of these cell expressions. In this study, the expression of the three study groups was obtained with the average number of cells that expressed different densities. Cell expression of VCAM-1 antibodies is expressed in endothelial cell membranes. Whereas, CD68 expression is expressed in the macrophage-specific cell cytoplasm. In endothelial dysfunction, after endothelialization is activated, there will be a process of recruitment of macrophage cells, neutrophils, and other pro-inflammatory cytokines. The inflammatory process will trigger the differentiation of monocyte cells into macrophage cells. However, it is not certain whether the macrophage cells that lead to endothelial dysfunction are resident macrophages or come from the bloodstream (Epelman et al. 2014). Macrophage cells can be identified by examination of CD68 antibodies expressed by macrophages in their cytoplasm.

Existing research so far discuss more about obesity in pregnancy, especially in trimester III BMI against inflammation in the placenta (Challier et al. 2008, Saben et al. 2014). Some researchers studied obesity BMI before pregnancy until the first trimester of pathological lesions in the placenta (Huang et al. 2014, Roberts et al. 2011). Previous studies have shown a link between obesity and the inflammatory process in the placenta that can influence fetal development by proving inflammatory cytokines on the umbilical cord. Whereas, in this study it can be proven that there is a relationship between obesity and weight gain on the metabolic processes of the fetus as seen through atherosclerosis markers in the fetal umbilical artery. Thus, it indirectly refers to the process of early atherosclerosis in the fetus that occurs in utero. Besides, in addition to being a marker of atherosclerosis, VCAM-1 is also a marker of other disorders, such as acute respiratory distress syndrome (ARDS) (Dewi et al. 2016).

One component that influences third trimester BMI is weight gain during pregnancy. Third trimester BMI shows more influence on atherosclerotic marker cell expression because the trimester III component of BMI is related to early pregnancy BMI and weight gain. Conditions of pregnancy with early obesity BMI cause early exposure to inflammation in the fetus, and when influenced by excessive weight gain, there will be an accumulation of inflammatory effects (Ingvorsen et al. 2014). Whereas, excessive body weight gain in the group with normal trimester I BMI despite being overweight caused a weaker effect seen in atherosclerotic marker cell expression in group II. The effect of BMI before pregnancy in overweight and obese mothers is greater than weight gain during pregnancy, despite having excessive weight gain (Choi et al. 2011).

In fetal outcomes, statistical analysis showed no relationship either to trimester III BMI or maternal weight gain during pregnancy. Previous research states that obesity in pregnancy increases the risk of pregnancy

complications, one of which is fetal growth abnormalities. Increased BMI of pregnant women above >30 kg/m^2 had a risk of giving birth to a macrosomic baby (≥4500 grams) for standard weight abroad 2 to 3 times higher (Leddy et al. 2008). A causal relationship between maternal obesity and fetal macrosomia was obtained with a dose dependent relationship. The incidence rate ranged from 13.3% in the obese group and 14.6% in the morbid obesity group. The study did not include data on gestational age at BMI at the time the study data was taken, so it is not clear whether trimester III BMI or weight gain caused large pregnancy outcomes during pregnancy (Leddy et al. 2008). Besides, excessive weight gain, especially specific in trimester 2 and trimester 3, has a greater risk of giving birth to a large baby during pregnancy (Crimmins et al. 2016, Karachaliou et al. 2015).

The results of this study differ from some research results abroad where in this study birth weight outcomes were obtained that did not differ from the three study groups. Statistically, it can be explained that the difference in the results of this study can be caused by the large sample size in the small group and the trimester I and trimester III BMIs that were not too high. In addition, the presence of other determinants influences the birth weight of babies so that the birth weight in the obese group is no different from the other groups. Third trimester BMI and weight gain are independent factors for determining a baby's birth weight that can be influenced by other independent factors. The existence of these factors can make the outcome of varying birth weight of infants where in large-scale studies other confounding factors can be analyzed better. Weight gain alone is quite difficult to monitor and is limited to specific gestational ages, especially at primary service level facilities. This is due to the non-uniform arrival of the patient at the specified gestational age, as well as the weight data of the first trimester pregnancy which are often only a media record or based on the patient's memory.

Results of the Apgar score both in the first minute and minute 5 did not differ between the three study groups. This is related to the selection of research subjects, where there were no maternal complications such as preeclampsia, chronic diseases and other immune disorders because they had been excluded in the determination of study samples. Thus, trimester III BMI and weight gain in pregnant women are risk factors for low Apgar score outcomes, if there is complication directly for the mother and baby. Low Apgar score outcomes in obese maternal infants increase in older maternal age, primipara, chronic hypertension, preeclampsia, gestational diabetes and pragestational (Persson et al. 2014). Another research states that maternal obesity affects fetal outcomes soon after birth in a number of different ways. Pregnancy complications alone play the most role in the Apgar score outcome in the first and fifth minutes (Zhu et al. 2015).

In this study there are several strengths of research. Obesity BMI was adjusted to Asian population standards so that it can represent the metabolic conditions of Indonesians, and analysis was done both in groups according to changes in BMI in trimester I and trimester III and based on trimester III BMI and weight gain analyzed. Whereas, the weakness of this study is the first trimester BMI was obtained from the recording of antenatal care books so that there might be differences in the size of the standard BMI of each study subject, and no weight gain measurements were taken in each semester of gestational age due to the limited source of weight gain data each semester.

CONCLUSION

Third trimester BMI and weight gain in obese pregnant women are associated with expression of atherosclerotic VCAM-1 and CD68 markers in the umbilical artery. However, trimester III BMI and weight gain in obese pregnant women are not associated with fetal outcomes.

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