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Research Article

ROLE OF MATERNAL SUBCUTANEOUS FAT THICKNESS IN THE PREDICTION OF GESTATIONAL HYPERTENSION/PRE-ECLAMPSIA

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ABSTRACT

Pre-eclampsia is one of the leading causes for increased morbidity and mortality for mothers and infants. Among the various risk factors identified to be associated with pre-eclampsia, obesity is the most important factor. Till date BMI has been used to measure obesity. This study was done to find correlation between maternal abdominal subcutaneous fat thickness and development of gestational hypertension/pre-eclampsia and to find a cut-off value of subcutaneous fat thickness for prediction of risk of developing gestational hypertension/pre-eclampsia.

Method: 200 women with live singleton pregnancy of 16-18 weeks gestation were included in the study after obtaining written informed consent and applying exclusion criteria. BMI, BP at 16-18 weeks and at 20-24 weeks was measured. Gestational hypertension/pre-eclampsia was diagnosed when BP was >140/90 mm of hg. Maternal abdominal subcutaneous thickness was measured by ultrasonography. Data were entered into MS excel sheet and analysed.

Results: Mean BMI and mean ASCFT in women who developed gestational hypertension/pre-eclampsia (25.75 ± 3.28 kg/m^{2}and 15.57 ± 2.95 mm respectively) were significantly more than in normotensive women (22.84 ± 2.93 kg/m^{2}and 12.05 ± 2.92 mm respectively). ROC curve analysis showed that ASCFT above 15.7 mm (AUC=0.801) predicted gestational hypertension/pre-eclampsia with a sensitivity of 62.5% and specificity of 86.9% and Youden index of 0.49. Using 15.7 mm cut - off value for ASCFT, the odd ratio of gestational hypertension/pre-eclampsia was 11.67 (95% CI 4.56-29.8492, p <0.0001).

Conclusion: Ultrasonographic measurement of SCFT will help us to identify women at high risk of developing gestational hypertension/pre-eclampsia.

INTRODUCTION

Preeclampsia, a pregnancy disorder, is defined as a systemic syndrome characterized by new-onset of hypertension (blood pressure – systolic >140 mm Hg, diastolic >90 mm Hg on two occasions at least 4 h apart, or in severe cases systolic blood pressure >160 mm Hg and diastolic blood pressure >110 mm Hg) and proteinuria (protein [mg]/creatinine [mg] ratio of >0.3 or protein >5 g in a 24 h urine sample, or >3 g in two samples taken 6 h apart from a patient on bed rest or with any features of end organ damage) after 20 weeks of gestational age in pregnant women, which resolves before the end of 6th week postpartum[1]. It affects up to 8% of all pregnancies worldwide and increases morbidity and mortality rates among both mothers and infants[2,3]. Pre-eclampsia is one of the important causes for preterm birth, low birthweight, stillbirth, low Apgar score and neonatal complications[4] so it is pertinent to identify risk factors for pre-eclampsia and to identify women who is at risk of developing pre-eclampsia in early pregnancy so as to monitor women frequently and give her aspirin prophylaxis. A wide range of pregnancy-specific characteristics (e.g. parity, placental factors, multi-fetal gestation, and excessive weight gain during pregnancy) and pre-existing maternal features (e.g. age, race, pre-pregnancy overweight or obesity, pre-pregnancy diabetes, chronic hypertension etc.) are considered to be associated with preeclampsia[5]. Out of them obesity is the most important factor for prediction of pre-eclampsia.

Prevalence of obesity is increasing day by day and in the USA in the last 30 years, the percentage of women who are obese (BMI > 30) or overweight (BMI > 25) has increased by 60%.[6] The WHO estimates that the female prevalence of overweight and obesity is 77% in the United States, 73% in Mexico, 69% in South Africa, 37% in France, 32% in China and 18% in India, with a wide variation within each continent.[7]

A strong direct correlation was found between an increasing body mass index (BMI) and the risk of developing preeclampsia and pregnancy induced hypertension.[8]Studies from different populations have consistently reported that elevated pre-pregnancy BMI is associated with an increased

risk of preeclampsia.[9]The adjusted risk of developing preeclampsia doubled for overweight mothers with a BMI of 26 kg/m^2, and almost tripled for obese mothers with a BMI of 30 kg/m^2.[10] Mission and colleagues reported a 0.82% rise in GDM with every 1 kg/m 2 rise of BMI and twofold rise in pregnancy-induced hypertension (PIH) with every 5–7 kg/m 2 rise of BMI[11].

Pre-pregnancy or early pregnancy body mass index is currently and most frequently used to measure obesity but it does not measure the degree of abdominal obesity, which is known to be associated with metabolic risk in non-pregnant populations[12,13]. The precise pathophysiologic connection between overweight and preeclampsia is not yet defined. However, several physiologic changes seen in both conditions have been suggested as possible contributors, such as elevated inflammatory responses[14], insulin resistance[15], modified levels of adipokines and oxidative stress[16].

Adipose tissue produces cytokines, chemokines, and adipokines. Leptin, kisspeptin, omentin-1, chemerin, ghrelin, visfatin, interleukin-6, resistin, tumor necrosis factor-alpha, and adiponectin belong to the adipokines[17]. Leptin, adiponectin, and kisspeptin are possibly responsible for diabetes mellitus and preeclampsia in obese pregnant women[18].Data from the Framingham Heart Study demonstrated that both visceral and subcutaneous fat volume are associated with an increased risk of metabolic syndrome, with visceral fat showing a stronger relation[13]. Greater maternal abdominal subcutaneous fat thickness has been shown to correlate with higher serum levels of hemoglobin A1C and C reactive protein in pregnant women[19].Suresh *et al*[20] and Kennedy *et al*[21] in their respective studies explored the utility of maternal abdominal subcutaneous fat thickness (SCFT) as a measure of abdominal obesity in pregnancy and as a predictor of pregnancy outcomes and observed that increase in ASCFT is associated with adverse pregnancy outcomes. ASCFT is highly correlated with obesity and can be measured by computer tomography (CT) and magnetic tomography (MR), both are very reliable methods[22]but CT is not a suitable choice for pregnant women due to the amount of radiation and MR is also not applicable because it is costly and time-consuming[23]. Measurement of abdominal subcutaneous fat by ultrasound is an easy, quick, non-invasive and cost-effective method and can be done at the same time as the routine ultrasound. It also avoids the use of ionizing radiation[24].This study was done to find correlation between maternal ASCFT and development of pre-eclampsia and to find a cut-off value of ASCFT for prediction of risk of developing pre-eclampsia.

MATERIAL AND METHODS

This was a descriptive observational study conducted in the Department of OB-Gy. 200 women with live singleton pregnancy of 16-18 weeks gestation were included in the study after obtaining written informed consent. Women with hypertension, type 1 or type 2 diabetes prior to pregnancy or with a previous history of GDMwere excluded. Pre-pregnancy BMI was calculated for all women. BP was measured at 16-18 weeks and 20-24 weeks of gestation. Ultrasonography was done to assess foetal well-being and rule out congenital malformation. Maternal abdominal subcutaneous thickness was measured from the subcutaneous fat layer to the outer border of the rectus abdominus muscle at the level of the linea alba. Three measurements were taken for subcutaneous thickness for each woman and mean subcutaneous thickness was determined. Pre-eclampsia was diagnosed when systolic BP >140 mm Hg, diastolic BP >90 mm Hg on two occasions at least 4 h apart, or in severe cases systolic blood pressure >160 mm Hg and diastolic blood pressure >110 mm Hg) and proteinuria (protein [mg]/creatinine [mg] ratio of >0.3 or protein >5 g in a 24 h urine sample, or >3 g in two samples taken 6 h apart or with other system involvement.

All data were entered into MS excel sheet and analysed. To determine the cut-off value for predicting gestational hypertension/pre-eclampsia a receiver operating characteristic (ROC) curve analysis was conducted, with the area under the curve (AUC), sensitivity, and specificity calculated. A logistic regression analysis was done to calculate the odds ratio for the ASCFT-mediated risk of gestational hypertension/pre-eclampsia. A p value 0.05 was considered to be statistically significant.

RESULTS

Out of 200 women included in the study, 24 (12%) women developed gestational hypertension/pre-eclampsia. Mean age of the women who developed gestational hypertension/pre-eclampsia (26.63 ± 3.02 years) was significantly more than mean age of normotensive women (23.82 ± 2.69 years) (p - 0.0000). Mean BMI and mean ASCFT in women who developed gestational hypertension/pre-eclampsia (25.75 ± 3.28 kg/m^{2}and 15.57 ± 2.95 mm respectively) were significantly more than in normotensive women (22.84 ± 2.93 kg/m^{2}and 12.05 ± 2.92 mm respectively) (Table 1)

Table 1 Age, BMI and ASCFT in normotensive women and with Pre-eclampsia

Variables	Total (n=200)	Normotensive (n=176)	Pre-eclampsia (n=24)	P value
Age (year)	24.17 ± 2.86	23.82 ± 2.69	26.63 ± 3.02	0.0000
BMI (kg/m²)	22.84 ± 2.93	22.43 ± 2.65	25.75 ± 3.28	0.0000
ASCFT (mm)	12.47 ± 3.13	12.05 ± 2.92	15.57 ± 2.95	0.0000

The mean BMI (Kg/m²) in the SCFT <15 mm group was 21.76 ± 1.99 Kg/m² and in the SCFT >15 mm group was 26.35 ± 2.76 Kg/m². Mean BMI in SCFT ≥15 mm was significantly more than in SCFT <15 mm (p <0.001). (Table 2)

Table 2 Association between SCFT (mm) and BMI (Kg/m²) (n = 200)

BMI (Kg/m²)	SCFT		p value
	<15 mm	>15 mm	
Mean ± SD	21.76 ± 1.99	26.35 ± 2.76	<0.001

Spearman Correlation) were used to explore the correlation between BMI and SCFT. There was a strong positive correlation between BMI (Kg/m²) and SCFT (mm), and this correlation was statistically significant (rho = 0.9, p = <0.001). For every 1 unit increase in BMI (Kg/m²), the SCFT (mm) increases by 0.97 units. Conversely, for every 1 unit increase in SCFT (mm), the BMI (Kg/m²) increases by 0.85 units. (Table 3 and Figure 1)

Table 3 Spearman Correlation between SCFT and BMI

Correlation	Spearman Correlation Coefficient	P Value
BMI (Kg/m²) vs SCFT (mm)	0.9	<0.001

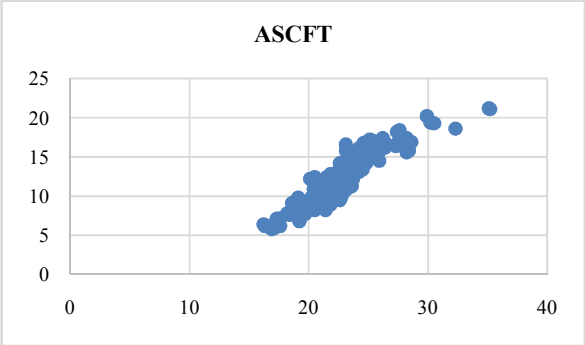

Figure 1 Correlation between BMI (Kg/m²) and SCFT (mm) (n = 200)

X axis: BMI; Y axis: SCFT

To find an effective cut-off value for predicting gestational hypertension/pre-eclampsia by ASCFT, a ROC curve analysis was conducted which showed that ASCFT above 15.7 mm (AUC=0.801) predicted gestational hypertension/pre-eclampsia with a sensitivity of 62.5% and specificity of 86.9% and Youden index of 0.49. At a cut off of 15.7 mm ASCFT had a positive predictive value of 39.5% and negative predictive value of 94.4%. (Table 4 and Figure 2)

Table 4 Receiver operating characteristic prediction curve analysis of variables

Predictor	AUROC	Sensitivity %	Specificity %	PPV (%)	NPV (%)	Youden Index	P value
ASCFT (cutoff: 15.7 mm by ROC)	0.801	62.5	86..9	39.5	94.4	0.49	<0.001

AUROC: Area under ROC curve, BMI: body mass index., ASCFT: abdominal subcutaneous fat thickness

Figure 2 ROC Curve Analysis showing Diagnostic Performance of SCFT (mm) in Predicting Preeclampsia(n = 200)

Increased BMI and abdominal SCFT was significantly associated with increased risk of developing gestational hypertension/pre-eclampsia. At 25 kg/m2 cut-off value for BMI, theodd ratio for developing gestational hypertension/pre-eclampsia was [12.29 (4.77 – 31.67), p <0.0001)] and using 15.7 mm cut-off value for ASCFT, the odd ratio for developing gestational hypertension/pre-eclampsia was 11.67 (95% CI 4.56-29.8492, p <0.0001). (Table 5)

Table 5 Association of ASCFT with risk of Pre-eclampsia

Variables	Pre-eclampsia		Odd Ratio, 95%CI	P value
	Yes (n=24)	No (n=176)		
ASCFT (mm)				
<15.7	9	154	11.67 (4.56-29.8492)	<0.0001
≥15.7	15	22		
BMI (Kg/m²)				
<25	10	158	12.29 (4.77 – 31.67)	<0.0001
>25	14	18		

DISCUSSION

This study was done to find association of maternal abdominal subcutaneous thickness with development of gestational hypertension/pre-eclampsia and it shows that increase thickness of SCFT measured at 16-18 weeks of pregnancy is associated with increased risk of development of gestational hypertension/pre-eclampsia. Very few studies have been done to find association of SCFT with pre-eclampsia.

In our study out of 200 women included, 24 (12%) women developed gestational hypertension/pre-eclampsia. The prevalence of gestational hypertension/pre-eclampsia in our study was higher than that observed by other studies done in the past.[25-27]

In the present study women who developed gestational hypertension/preeclampsia were older (26.63 ± 3.02 vs. 23.82 ± 2.69 years) than normotensive women. Our observation was in line with observation made by Shao Y *et al*[9] and in contrast with observation made by Pétursdóttir Maack *et al*[26]. In the current study women who developed gestational hypertension/preeclampsia had a significant higher BMI (25.75 ± 3.28 vs. 22.43 ± 2.65 kg/m2) (p -0.0000) and a significantly higher ASCFT (15.57 ± 2.95 vs. 12.05 ± 2.92 mm) than in normotensive women. which is in line with observation made by Pétursdóttir Maack *et al*[26]. They observed that women who developed gestational hypertension/ preeclampsia had higher BMI in early pregnancy (26.8 ± 5.5 vs. 25.1 ± 4.8 kg/m2). Pétursdóttir Maack *et al*[27] in their study observed that women who developed pre-eclampsia had significantly higher BMI and subcutaneous fat thickness (27.5±6.5 kg/m2 vs. 25.0±4.9 kg/m and 2.04±0.89 cm vs. 1.65±0.73 cm respectively).

We observed that mean BMI in women with SCFT ≥15 mm was significantly more than in women with SCFT <15 mm (p <0.001). Our observation was consistent with the observation made by Kosus N *et al* where mean BMI was significantly more in women with SCFT >15mm (27.34 ± 4.15 Kg/m²) than in women with SCFT <15 mm (23.88 ± 3.12 Kg/m²) (p <0.001)[19].In our study BMI and SCFT had a strong positive correlation which was statistically significant (rho = 0.9, p=<0.001). Our observation was consistent with observation made by Kosus N *et al*[19], Suresh A *et al*[20], Eley *et al*[28], Lindberger E *et al*[29] and Kansu-Celik H[30]. All of them observed that BMI and SCFT were highly correlated. Kennedy *et al*[21] in their study also demonstrated a significant correlation between BMI and SCFT (p=<0.00).

In our study we found that compared to women with normal pre-pregnancy BMI, those who were overweight/obese had an increased risk of gestational hypertension/pre-eclampsia [OR 12.29, (95%CI: 4.77 – 31.67;p - <0.001). Our results were in line with observation made by various authors in their studies. Shao Y *et al* in their study observed that overweight/obese had an increased risk of preeclampsia compared to women with normal BMI (OR = 1.81; 95%CI: 1.37–2.39)[9].Cedergren MI observed a 5-fold increase in risk of preeclampsia among the morbidly obese women[31].Bhattacharya S *et al* in their studies observed that both pre-eclampsia and gestational hypertension increased linearly with increasing BMI, resulting in an adjusted Odds Ratio of 7.2 (95% CI 4.7, 11.2) for pre-eclampsia and 3.1 (95% CI 2.0, 4.3) for gestational hypertension in the morbidly obese category when compared to those of normal BMI[32].Athukorala C *et al* observed that

obese women were at higher risk of developing pregnancy induced hypertension (PIH) (RR 3.19 [95%CI 2.36, 4.30]) and pre-eclampsia compared with women with a normal BMI (RR 2.99 [95%CI 1.88, 4.73)], p < 0.0001)[33].Van Der Linden EL *et al* observed that women with obesity had more than a six-fold higher risk to develop PIH (RR 6.17, 95% CI 2.90 to 13.13)[34].

In present study women with >15.7 mm SCFT had increased risk of developing gestational hypertension/pre-eclampsia [OR 11.67, 95% CI: (4.56-29.8492), p- <0.0001]. Our observations were similar to very few studies done in the past. Suresh A *et al* in their study observed that every 5-mm higher value in SFT increased the odds for cumulative adverse pregnancy outcome (gestational diabetes mellitus, pre-eclampsia, gestational hypertension, instrumental deliveries, caesarean delivery, preterm delivery, macrosomia, small for gestational age, 5-min Apgar score < 7, low birth weight, intrauterine growth restriction, antepartum haemorrhage, and premature rupture of membranes) by 4 % and concluded that SFT is more strongly associated with the risk of developing adverse pregnancy outcomes than general adiposity as measured by BMI[20].In a study done by Kennedy *et al* increase in SCFT is associated with increased risk of hypertensive disease [OR 1.33; 95%CL: 1.21–1.47; p <0.00][21]. Pétursdóttir Maack, H *et al* observed that women with greater SAT thickness more often developed pre-eclampsia, OR 1.79 (95% CI 1.48–2.17), i.e. with every centimetre increase in SAT thickness, the risk of pre-eclampsia increased by 79%[27].

CONCLUSIONS

Our study shows that women with abdominal SCFT >15.7 mm at 16-18 weeks of pregnancy had 11.67-fold increase risk of developing gestational hypertension/pre-eclampsia. Ultrasonographic measurement of SCFT is a quick, economic and reliable method and will help us in identifying women who are at risk of developing gestational hypertension/pre-eclampsia. SCFT can be used as surrogate marker to identify women at risk of gestational hypertension/pre-eclampsia.

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