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Predictive analysis of maternal subcutaneous fat thickness for the risk of foetal macrosomia

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Abstract

Introduction: Foetal macrosomia is defined as a birth weight above the 90th percentile for gestational age or a birth weight ≥4000 g. Maternal obesity is one of the risk factors for foetal macrosomia. Maternal abdominal subcutaneous fat thickness can be used as a marker for central obesity. This present study was done to find association of maternal BMI and abdominal SCFT with macrosomia and to find a cut-off value of BMI and SCFT for prediction of macrosomia.

Methods: 200 women, with live singleton pregnancy of 16-18 weeks of gestation were included after written informed consent. Maternal abdominal subcutaneous thickness was measured by ultrasonography. Women were followed till delivery and birth weight was calculated and babies with birth weight >4000 gm were diagnosed to be macrosomic. Data were analyses.

Results: Spearman correlation between SCFT and neonatal weight shows a significant but weak positive linear relation (r= 0.4325, p- 0.000). Mean SCFT was significantly more in women with macrosomia (17.26 ± 2.6 vs. 12.35 ± 3.05 mm, p 0.0005 respectively) ROC curve analysis for ASCFT showed that ASCFT above 14.3 mm (AUC=0.970) predicted macrosomia with a sensitivity of 100% and specificity of 73%. Increased abdominal SCFT was significantly associated with increased risk of developing macrosomia. Using 14.3 mm cut -off value (by ROC curve) for ASCFT, the odd ratio of macrosomia was 30 (95% CI 1.6341-553.2106, p 0.02).

Conclusion: Our study found that measurement of SCFT at 16-18 weeks is a significant predictor of macrosomia.

Keywords: Obesity; Macrosomia; Ultrasonography; Subcutaneous Fat Thickness

1 Introduction

Foetal macrosomia is defined as a birth weight above the 90th percentile for gestational age or a birth weight greater than or equal to 4000 g; however others use 4500 g as the cut point [1]. Foetal macrosomia is seen in 12% of newborns of normal women and 15-45% of newborns of women with gestational diabetes mellitus (GDM) [2]. Excessive growth in the foetus is a major contributor to adverse obstetrical outcomes. Khashu et al. examined the perinatal outcomes of 1842 macrosomic newborns in British Columbia, and Canada and identified significantly increased maternal risks of emergency Caesarean section, obstetrical trauma, postpartum hemorrhage, and maternal diabetes (all outcomes, $P < 0.001$) [3]. Further, the infants were at higher risk of having birth trauma, of needing resuscitation, and of having an Apgar score less than seven at five minutes of life ($P < 0.001$) [3]. There is also evidence that macrosomia is associated

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with shoulder dystocia, brachial plexus injury, skeletal injuries, meconium aspiration, perinatal asphyxia, hypoglycemia, and foetal death [4].

Maternal obesity has a strong and independent effect on foetal macrosomia [5]. Gestational age at delivery, maternal pre-pregnancy body mass index (BMI), pregnancy weight gain, maternal height, hypertension and cigarette smoking also have a significant impact. When obese women were compared to normal-weight women, the newborns of obese women had more than double the risk of macrosomia compared to those of women with normal weight [6]. In a study from Finland, the risk of macrosomia and cesarean delivery was higher in obese women with and without GDM than in normal-weight women with and without GDM [7]. Maternal obesity has been found to be associated with increased cord C-peptide concentration as a marker of foetal hyperinsulinemia and neonatal adiposity as a marker of macrosomia [8,9].

The prevalence of obesity has increased considerably among women of reproductive age in the last decades in both high and middle income countries [10]. The presence of obesity-associated health issues varies among individuals with obesity [11]. In general, the risk increases with increasing BMI [12]. It is known that central adiposity is a stronger predictor of obesity-related complications, such as type 2 diabetes mellitus and cardiovascular disease, than is general adiposity [13].

Historically, fat was considered to cushion and insulate the body; however, more recently its critical role in the human body as a form of energy storage and endocrinological signalling has been recognised [14]. With the escalating incidence of obesity, a better understanding of fat metabolism and advanced techniques to quantify and characterise adiposity are necessary. Some recent studies demonstrated that subcutaneous adiposity is associated with insulin resistance [15, 16]. A recent study revealed that increased biological activity in the SAT of pregnant women was associated with inflammation. The secretion of inflammatory agents, for example, leptin, adiponectin, and retinol-binding protein-4, was detected higher in subcutaneous tissue than in visceral adipocytes [17]. In addition, it was shown that increased inflammation and cytokines produced by fat tissue induce insulin resistance [18]. It is hypothesized that maternal insulin resistance and increased plasma glucose levels triggers hyperinsulinemia in the foetus, which stimulates foetal growth [19]. Higher plasma glucose levels also result in more energy available for the foetus [20].

Currently, BMI in early pregnancy is used for prediction of adverse pregnancy outcome in overweight and obese women [21]. However, this method is not optimal since BMI does not describe fat distribution or the proportion of adipose to non-adipose tissue [22, 23]. Central abdominal obesity (adipose tissue around the trunk) increases the risk of cardiovascular disease, hypertension and diabetes, whereas peripheral adiposity (adipose tissue around the bottom and thighs) appears to be protective [23].

Central obesity can be assessed by several techniques, for example WC, WHR, ultrasonography, bioelectrical impedance analysis, dual energy X-ray absorptiometry, computed tomography (CT) and magnetic resonance imaging (MRI) [14]. Computed tomography and MRI are the golden standard methods for measuring visceral fat (cross sectional or volumetric measurement) [14]. However, CT is not suitable for assessment of body fat distribution during pregnancy because of ionizing radiation, and MRI is both expensive and time consuming [23]. Maternal abdominal subcutaneous fat thickness (SCFT) can be used as a surrogate measure for central obesity and is readily and accurately measured by ultrasound, a quick, safe modality used routinely in pregnancy [24,25]. 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. [26] Recently, the utility of maternal abdominal subcutaneous fat thickness (SCFT) as a measure of abdominal obesity in pregnancy and as a predictor of pregnancy outcomes has been explored [23, 27]. Suresh et al retrospectively studied 1200 nulliparous women and found an ultrasound measurement of abdominal SCFT was better than BMI at predicting gestational diabetes, caesarean delivery and large-for-gestational- age neonates. [27] Kennedy et al prospectively studied 1385 women and concluded that SCFT was a significant independent predictor of adverse pregnancy outcomes [20]. Till date very few studies have been done to find association of SCFT with macrosomia. This present study was done to find association of maternal BMI and abdominal SCFT with macrosomia and to find a cut-off value of BMI and SCFT for prediction of macrosomia.

2 Material and methods

This was a prospective observational study conducted in the Department of Ob -Gy. 200 women, who were willing to participate in the study, with live singleton pregnancy of 16-18 weeks of gestation were included after written informed consent. Women with hypertension, type 1 or type 2 diabetes prior to pregnancy or with a previous history of GDM were excluded. Pre-pregnancy weight was asked and BMI was calculated. 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. Women were followed till delivery and birth weight was calculated and babies with birth weight >4000 gm were diagnosed to be macrosomia.

On the basis of BMI women were grouped as: Underweight: BMI <18.5 Kg/m^2 Normal weight: BMI – 18.5 – 24.9 Kg/m^2 Overweight: BMI – 25 – 29.9 Kg/m^2 Obese: BMI - ≥30 Kg/m^2

All data were entered into MS excel sheet and analysed. To determine the cut-off value for predicting macrosomia 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 SCFT-mediated risk of macrosomia. A p value 0.05 was considered to be statistically significant.

3 Results

Out of 200 women, 13 (6.5%) women were under weight, 156 (78.0%) were normal weight, 26 (13.0%) were overweight and 5 (2.5%) women were obese. Age of the women and SCFT were significantly associated with BMI. Occurrence of macrosomia was significantly more in overweight (11.5%) and obese (20%) women compared to normal (0.6%) and underweight (0.0%) women (p 0.002). (Table 1)

Table 1 Association between BMI and various parameters

Parameters	BMI (Kg/m^2)				P value
	<18.5 (n=13)	18.5 – 24.9 (n=156)	25 – 29.9 (n=26)	≥30 (n=5)	
Age (Years)	20.31 ± 1.32	24.12±2.32	26.96 ± 2.24	27.41±1.51	<0.001
SCFT (mm)	6.60 ± 0.67	12.38±1.58	16.61 ± 1.15	20.13±0.26	<0.001
Macrosomia (Yes)	0 (0.0%)	1 (0.6%)	3 (11.5%)	1 (20%)	0.002

Spearman correlation between BMI and age, SCFT and birth weight was calculated and it was found that BMI had a moderate positive correlation with age which was statistically significant (r=0.6663, p- 0.000) and a significant but weak positive linear relation with neonatal birth weight (r= 0.4481, p- 0.000). BMI and SCFT had a high positive and significant correlation (r= 0.8977, p- 0.000). Spearman correlation between woman's SCFT and neonatal weight shows that there was a significant but weak positive linear relation (r= 0.4325, p- 0.000). (Table 2, Figure 1-4)

Table 2 Spearman correlation between BMI and Age, SCFT, Birth weight

Correlation	Spearman Correlation Coefficient	P Value
BMI (Kg/m^2) vs Age of the woman (years)	0.6663	0.000
BMI (Kg/m^2) vs SCFT (mm)	0.8977	0.000
BMI (Kg/m^2) vs Birth weight (Kg)	0.4484	0.000
SCFT (mm) vs Birth weight (Kg)	0.4325	0.000

Table 3 Age, BMI and SCFT in women with or without macrosomia

Variables	Total (n=200)	Macrosomia (n=5)	Without macrosomia (n=195)	P value
Age (year)	24.17 ± 2.86	27.4 ± 2.41	24.08 ± 2.82	0.009
BMI (kg/m^2)	22.84 ± 2.93	28.16 ± 4.04	22.7 ± 2.78	0.0000
SCFT (mm)	12.47 ± 3.13	17.26 ± 2.6	12.35 ± 3.05	0.0005

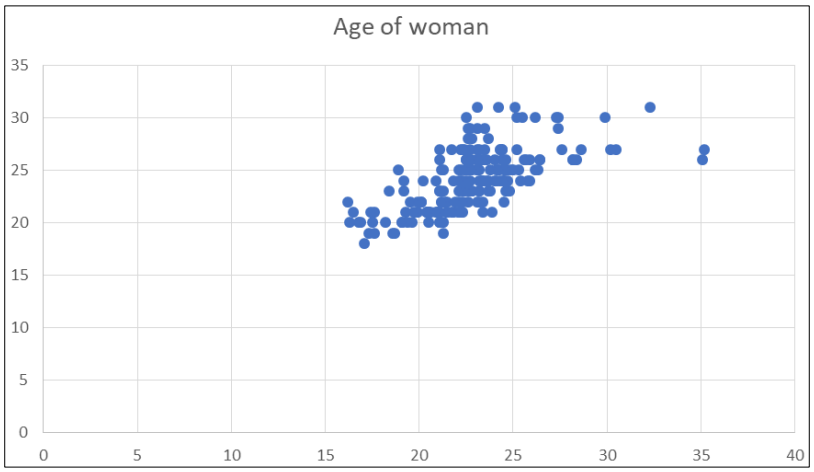

Figure 1 Correlation between BMI (X-axis) and Age of the woman (Y -axis)

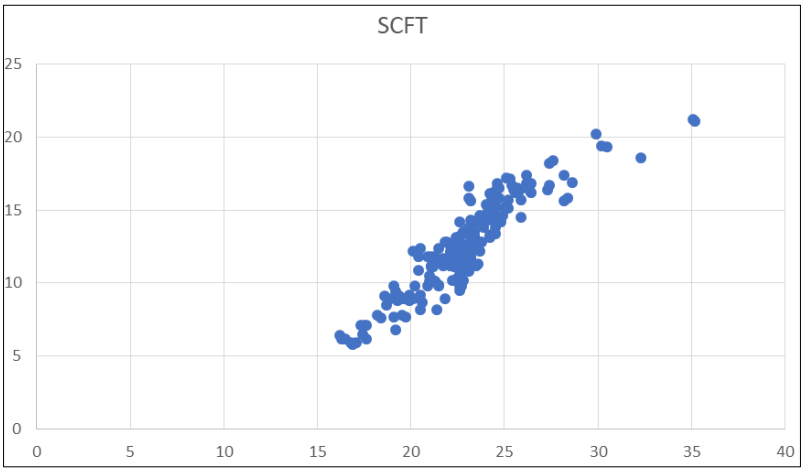

Figure 2 Correlation between BMI (X-axis) and SCFT (Y -axis)

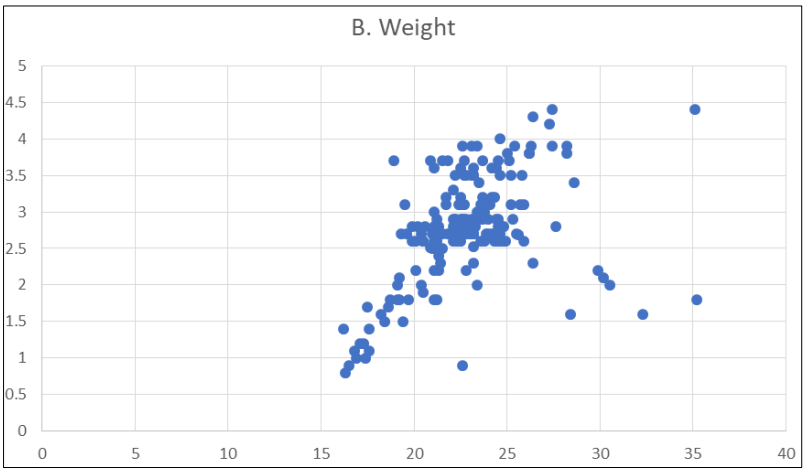

Figure 3 Correlation between BMI (X-axis) and Birth weight (Y axis)

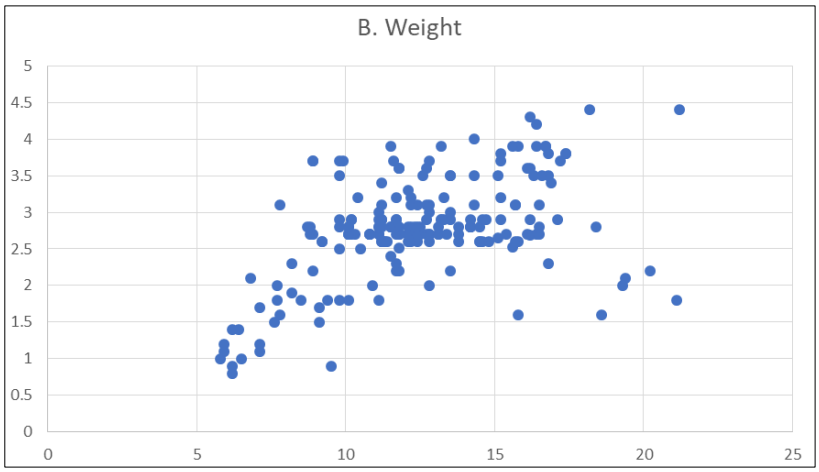

Figure 4 Correlation between SCFT (X-axis) and Birth weight (Y axis)

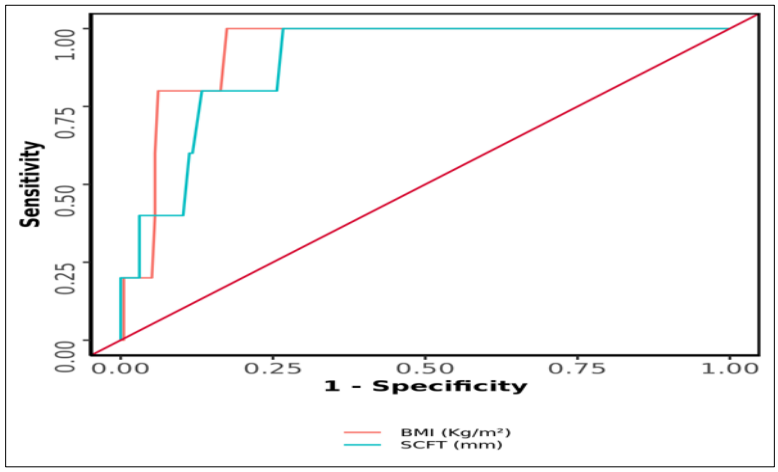

Figure 5 Receiver operating characteristic curve analysis of BMI and SCFT for prediction of macrosomia

Mean age of the women with macrosomia babies (27.4 ± 2.41 years) was significantly more than women without macrosomia (24.08 ± 2.82 years) (p 0.009). Mean BMI and Mean SCFT were significantly more in women with macrosomia (28.16 ± 4.04 vs. 22.7 ± 2.78 kg/m^2, p 0.0000 and 17.26 ± 2.6 vs. 12.35 ± 3.05 mm, p 0.0005 respectively) (Table 3).

To find an effective cut-off value for predicting macrosomia by BMI and ASCFT, a ROC curve analysis was conducted which showed that pre-pregnancy BMI above 24.6 kg/m^2 (AUC=0.931) predicted macrosomia with a sensitivity of 100% and specificity of 83% and Youden index of 0.83. ROC curve analysis for ASCFT showed that ASCFT above 14.3 mm (AUC=0.970) predicted macrosomia with a sensitivity of 100% and specificity of 73% and Youden index of 0.73. There was no significant difference in the diagnostic performance of BMI (Kg/m^2) and SCFT (mm) in prediction of macrosomia (DeLong's Test p = 0.129). (Table 4 and Fig 5)

Table 4 Receiver operating characteristic curve analysis of BMI and SCFT for prediction of macrosomia

Predictor	AUROC	Sensitivity %	Specificity %	PPV (%)	NPV (%)	Youden Index	P value
BMI (Kg/m^2)	0.931	100	83	13	100	0.83	<0.001
SCFT (mm)	0.895	100	73	9	100	0.73	<0.001

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

Increased BMI was significantly associated with increased risk of developing macrosomia. BMI at a cut-off value of 25 kg/m^2 was associated with approximately 25 times increased risk of macrosomia. BMI at a cut-off 24.6 kg/m^2 (by ROC curve) was associated with approximately 50 times increased risk of macrosomia. Increased abdominal SCFT was significantly associated with increased risk of developing macrosomia. Using 14.3 mm cut -off value (by ROC curve) for ASCFT, the odd ratio of macrosomia in 200 women screened was 30 (95% CI 1.6341-553.2106, p 0.02). (Table 5)

Table 5 Association of BMI and ASCFT with risk of Macrosomia

	Macrosomia		**Odd Ratio, 95%CI**	**P value**
	Yes (n=5)	**No (n=195)**		
BMI (kg/m^2)				
<25	1	168	24.88 (2.6797-231.1649)	0.004
≥25	4	27		
BMI (kg/m^2)				
<24.6	0	160	49.73 (2.6880-920.1180)	0.008
>24.6	5	35		
ASCFT				
<14.3 mm	0	143	30 (1.6341-553.2106)	0.02
≥14.3 mm	5	52		

4 Discussion

The occurrence of macrosomia in our study was 2.5% which was higher than the rate of 1.8% by Tsai Y L et al [28] and less than the rate of 3.1% reported by Nielsen et al [29] and 9.1% reported in a Scottish study [30]. In our study macrosomia was seen in 0.6% of normal weight women, in 11.5% and 20% of overweight and obese women respectively. Our results were consistent with observation made by Owens LA et al [31]. The occurrence of macrosomia was more in their study compared to ours but percentage of macrosomia in overweight and obese women (21.4% and 27.8% respectively) was higher than in normal weight women (15.5%) [31].

In our study BMI showed a positive linear but significant relation with age and birth weight. In contrast to our study Owens LA et al observed that there was no correlation between increasing maternal age and increasing BMI but there was a linear increase in birth weight across each BMI group [31]. We also observed a strong positive correlation between BMI and SCFT which was consistent with observation made by Lindberger E et al [11], Kennedy et al [23], Suresh A et al [27], Kosus N et al [32], and Eley et al [33]. We also observed a moderate positive correlation between foetal Weight and SCFT, and this correlation was statistically significant (rho = 0.43, p = <0.001). Our results were consistent with that of Lindberger E et al [11] and Kosus N et al [32].

Mean age of the women in our study was 24.17 ± 2.86 years which lower than mean age observed in the studies done by Kennedy et al [23], Suresh A et al [27], Eley et al [33] , Sommer C et al [34] and Van Der Linden EL et al [35]. This may be due to early marriage which is still common in our state. In our study as BMI increased there was increase in SCFT being lowest in BMI <18.5 Kg/m2 group and highest in BMI 35.0-39.9 Kg/m2. Our results were in line with observation made by Kennedy et al [23] in their study. Mean BMI of the women in our study were lower than mean BMI of the women observed by Ijäs H et al [7] and Catalano PM et al [9].

In the present study increased BMI was significantly associated with increased risk of developing macrosomia. BMI at a cut-off value of 25 kg/m^2 was associated with approximately 25 times increased risk of macrosomia. BMI at a cut-off 24.6 kg/m^2 (by ROC curve) was associated with approximately 50 times increased risk of macrosomia. Increased abdominal SCFT was significantly associated with increased risk of developing macrosomia. Using 14.3 mm cut -off value (by ROC curve) for ASCFT, the odd ratio of macrosomia was 30 (95% CI 1.6341-553.2106, p 0.02). Our results were in line with that of Kennedy et al [23] where a significant association was seen between Macrosomia and high SCFT (p= <0.00). Ijäs H et al [7], Van Der Linden EL et al [35], Athukorala C et al [36], and Yu et al [37] also observed increase risk of macrosomia in women with overweight and obesity. Bhattacharya S et al [38] observed that macrosomia

was more common in the obese and morbidly obese groups with Odds Ratios of 1.9 (95% CI 1.6, 2.2) and 2.1 (95% CI 1.3, 3.2) respectively, compared to the normal BMI group. Miao M et al [39] observed an odd ratio of 8.04 (3.46–18.66) for macrosomia in their study. Tsai Y L et al [28] observed that overweight women had a nine-fold increased risk of delivering an infant with macrosomia. Lindberger E et al [11] did not find any association between subcutaneous fat and birthweight or LGA after adjustments for covariates.

In our study ROC curve analysis was conducted which showed that pre-pregnancy BMI above 24.6 kg/m^2 (AUC=0.931) predicted macrosomia with a sensitivity of 100% and specificity of 83% and Youden index of 0.83. ROC curve analysis for SCFT showed that SCFT above 14.3 mm (AUC=0.970) predicted macrosomia with a sensitivity of 100% and specificity of 73% and Youden index of 0.73. Various mechanisms proposed to explain the association between maternal overweight and foetal overgrowth or macrosomia. Maternal overweight/obesity can change the inflammatory response, resulting in increased concentration of TNF-α, IL-1b and IL-6, and leptin and then worsening insulin resistance and foetal overgrowth [40]. Further, a study reported that leptin enhances the activity of the amino acid transporter system A that is among the primary determinants for the supply of nutrients to the foetus [41]. In addition, being overweight/obese also increases the risk of GDM, which further increases the risk of macrosomia. Pedersen's hypothesis states that maternal hyperglycemia can be transported to the foetus via the placenta but insulin could not [41]. The hyperglycemia in the foetus stimulates secretion of insulin in the foetus, which leads to fat accumulation in the foetus [42].

5 Conclusion

Our study found that measurement of SCFT at 16-18 weeks is a significant predictor of macrosomia. Till date we were using maternal pre-pregnancy BMI to predict the risk of adverse pregnancy outcome so ultrasonographic measurement of SCFT can be used as a marker to identify women at high risk of macrosomia.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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