

## ORIGINAL ARTICLE

## Changes in adipose tissue distribution during pregnancy in overweight and obese compared with normal weight women

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**OBJECTIVE:** Differences in body fat distribution contribute to the metabolic abnormalities associated with overweight and obesity; however, such differences have not been adequately explored during pregnancy. Our aim was to compare longitudinal trends in maternal abdominal adipose tissue deposition during pregnancy in overweight/obese compared with normal weight women.

**STUDY DESIGN:** Pregnant women, classified as normal weight (body mass index (BMI)  $< 25 \text{ kg m}^{-2}$ ;  $N = 61$ ) or overweight/obese (BMI  $\geq 25 \text{ kg m}^{-2}$ ;  $N = 57$ ), were enrolled in a prospective cohort study starting in the first trimester. Maternal subcutaneous (smin) and preperitoneal (pmax) fat were measured by ultrasound at five time points starting between 6 and 10 weeks gestation. The abdominal fat index (AFI), an established marker of visceral adipose tissue, was calculated as the ratio of pmax to smin. The trajectories of smin, pmax, cumulative fat index (smin plus pmax) and the AFI across pregnancy were analyzed using mixed linear models.

**RESULTS:** The rate of maternal weight gain during pregnancy was significantly lower for overweight/obese women compared with their non-overweight counterparts ( $P < 0.05$ ). Accordingly, the rate of change of pmax and smin differed significantly in normal weight compared with overweight/obese women ( $P = 0.0003$  and  $0.01$ , respectively). The cumulative fat index did not change across gestation in normal weight women, whereas it decreased for overweight/obese women ( $P = 0.0005$ ). The log AFI increased across pregnancy in both strata, but significantly more rapidly for normal weight compared with overweight/obese women ( $P = 0.06$ ).

**CONCLUSIONS:** Adipose tissue is preferentially deposited in the more metabolically active visceral compartment as pregnancy progresses. However, this process differs in normal weight compared with overweight/obese women and may contribute to metabolic differences between these groups. Our study is a step toward a more refined description of obesity and its consequences during pregnancy.

*Nutrition & Diabetes* (2013) 3, e84; doi:10.1038/nutd.2013.25; published online 26 August 2013

**Keywords:** abdominal fat index; adiposity; longitudinal; obesity; visceral fat

## INTRODUCTION

Maternal obesity is a major public health concern that is associated with poor outcomes for both the mother and the developing fetus.<sup>1</sup> Obesity may simply be characterized by the presence of excessive amount of adipose tissue. However, an increase in maternal adipose tissue is also an important adaptive response to pregnancy. Work in non-pregnant adults suggests that obesity is characterized by a distinct metabolic state that may ultimately be responsible for associated health problems, including increased risk of type 2 diabetes, fatty liver and cardiovascular disease.<sup>2</sup> During pregnancy, this maternal metabolic state may affect maternal health, fetal growth and 'program' a set of physiologic responses in the fetus that predisposes offspring to metabolic and cardiovascular disease later in life.<sup>3,4</sup> Crude metrics, such as body mass index (BMI), fail to acknowledge the many relationships among factors that give rise to this obese state.<sup>5</sup> To properly understand maternal obesity and its consequences, more refined descriptions of the obese state during pregnancy are needed to predict which women are at highest risk for adverse obesity-related outcomes.

In non-pregnant adults, body fat distribution is one important factor underlying the metabolic abnormalities associated with obesity.<sup>6,7</sup> The deposition of adipose tissue occurs in two different anatomic depots: visceral adipose tissue (VAT) and subcutaneous adipose tissue (SCAT). VAT, located around abdominal viscera in the mesentery and omentum, differs from SCAT<sup>8</sup> in its endocrine function, lipolytic activity and immunologic function.<sup>8,9</sup> As a result, VAT has an important role in metabolic and inflammatory responses associated with adiposity.<sup>10</sup> In non-pregnant adults, VAT deposition is associated with a greater risk of diabetes, dyslipidemia and accelerated atherosclerosis than SCAT accumulation.<sup>11</sup> It may be that the effects of obesity on pregnancy outcomes are also mediated by the differences in metabolic and physiologic abnormalities arising from differences in VAT deposition. Despite its importance, few studies have investigated how the distribution of adipose tissue changes during pregnancy.<sup>12</sup>

A number of techniques for evaluating abdominal fat distribution have been developed.<sup>13</sup> Anthropometric measurements, such as waist circumference and waist-to-hip ratio, are often used as indirect measurements of visceral fat in non-pregnant adults.

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Received 16 July 2013; accepted 20 July 2013

However, these measurement methods do not differentiate between VAT and SCAT and have not been validated during the pregnancy. Among the direct methods, computed tomography and dual energy x-ray absorptiometry are considered the most accurate and reproducible methods to assess abdominal fat. However, both of these methods are costly, time consuming and expose patients to ionizing radiation. The accompanying teratogenic risks make them infeasible during pregnancy.<sup>14</sup> Magnetic resonance imaging (MRI) has more recently been used but is time-consuming and expensive. A few recent studies have used bioelectrical impedance analysis to estimate body composition.<sup>15</sup> Although bioelectrical impedance analysis can distinguish between fat and fat-free mass, it does not specifically measure the relative quantities and distribution of VAT and SCAT, important correlates of metabolic disease and its associated pathologies. Moreover, changes in body-composition characteristics during pregnancy, such as hydration and edema, may affect the validity of the interpretation of impedance measurements.

In contrast, measurement of the abdominal fat index (AFI) using ultrasound measures of adipose tissue in the upper abdomen is a simple, non-invasive and safe method to estimate VAT and adipose tissue distribution.<sup>16</sup> The AFI—defined as the ratio of maximum preperitoneal fat (pmax) to minimum subcutaneous fat (smin)—has been validated against abdominal computed tomography estimates of VAT and shown to be associated with metabolic markers such as insulin and circulating lipid levels in non-pregnant adults.<sup>16</sup> Thus, the AFI is a good surrogate measure of VAT. Studies with small sample sizes ( $N < 35$ ) have started to document changes in AFI across pregnancy.<sup>17,18</sup>

Our aim was to use ultrasound measures to characterize longitudinal trends in maternal abdominal adipose tissue deposition during pregnancy in overweight/obese women compared with their normal weight counterparts. These analyses are the first step toward defining how the differences in the regional distribution of adipose tissue between overweight/obese and normal weight women may contribute to metabolic dysregulation and adverse pregnancy outcomes associated with maternal obesity.

## MATERIALS AND METHODS

### Study sample

Data were collected as part of the Gestational Regulators of Weight (GROW) study, a prospective cohort study of pregnant women who presented for early prenatal care at the University of Michigan Health System (UMHS). The UMHS Institutional Review Board approved this study. Women were eligible if they were 18–45 years of age, had a singleton pregnancy and intended to deliver at the study hospital. Participants were seen at 6–10, 10–14, 16–20, 22–26 and 32–36 weeks gestation. Data collected at each of the five study visits included a brief interview, anthropometric measurements and ultrasound measurements; additional information was collected through medical record abstraction.

Baseline maternal demographic and health characteristics were collected by questionnaire upon entry into the study and by subsequent review of medical records. Changes in maternal health characteristics were assessed at each subsequent time point. Standing height was measured using a stadiometer. Weight was measured at each time point in light street clothes, without shoes, on a calibrated electronic scale (Scale-tronix Inc., White Plains, NY, USA). Maternal prepregnancy weight was collected by self-report at the initial visit. Prepregnancy BMI was calculated using height and prepregnancy weight ( $\text{BMI} = \text{kg m}^{-2}$ ), and was categorized into two levels using World Health Organization (WHO) cutoff points as normal weight ( $< 25.0 \text{ kg m}^{-2}$ ) and overweight/obese ( $\geq 25.0 \text{ kg m}^{-2}$ ), based on the most recent recommendations of the Institute of Medicine.<sup>19</sup>

As the weight of the fetus comprises a significant percentage of gestational weight gain, use of total weight gain may overestimate tissue accretion and weight gain by the mother. One strategy to address this issue is to use net maternal weight gain, calculated by subtracting the estimated fetal weight from maternal weight to remove artificial structural biases from the association between birth weight and maternal weight gain. For all analyses, the maternal weight at each study visit was therefore

corrected by subtracting the estimated fetal weight, determined by ultrasound biometry using the method of Hadlock *et al.*<sup>20</sup> The corrected maternal weight is designated as the effective maternal weight.

Abdominal fat distribution was assessed by ultrasound using the method described by Suzuki *et al.*<sup>16</sup> Maternal subcutaneous (smin) and preperitoneal (pmax) fat were measured in triplicate at each study visit. Measurements were performed with study participants in the supine position. The ultrasound transducer was held perpendicular to the skin at the midline of the upper abdomen just below the xyphoid process and with minimal pressure. Participants held their breath during the measurement to minimize the effects of the respiratory movements on liver position. The thickness of the subcutaneous and preperitoneal fat layers was measured with electronic calipers; the linea alba was not included in the calipers. The AFI was calculated as the ratio of pmax to smin.<sup>16</sup> Data were not normally distributed; therefore, the AFI was log transformed. Triplicate measures of the log-transformed AFI were averaged.

### Statistical analysis

Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). Hypothesis tests were two-tailed with a type 1 error rate fixed at 5%. Differences between BMI groups (interaction terms) were assessed using a type 1 error rate of 10%.<sup>21</sup> Demographic and health-related characteristics of the study population were compared using  $\chi^2$  tests and Fisher's exact test as appropriate. Log-transformed AFI measures of normal weight and overweight/obese women at each study visit were compared using *T*-tests. The trajectories of cumulative maternal weight gain (effective maternal weight at each study visit minus prepregnancy weight), smin, pmax, smin plus pmax (cumulative fat index) and the AFI across pregnancy were analyzed using mixed linear models. An interaction term between BMI and time was included to estimate differences in the rate of change of the measurements over the course of pregnancy for both BMI groups. Mixed linear models consider the longitudinal structure of the variables, thus allowing the data to exhibit correlation and non-constant variability by including both fixed-effect and covariance parameters. The mixed linear modeling procedure used here implements a likelihood-based estimation method so that all available data are used in the analysis without excluding subjects with data missing at one or more time points.

## RESULTS

Table 1 presents the sociodemographic and health characteristics of the 118 participants who had abdominal fat measurements during the study. Characteristics are stratified on maternal prepregnancy BMI categorized as normal weight ( $< 25.0 \text{ kg m}^{-2}$ ) and overweight/obese ( $\geq 25.0 \text{ kg m}^{-2}$ ). There were no significant differences between the strata with respect to sociodemographic characteristics. However, there is considerable variation in prepregnancy BMI. Our sample was almost equally distributed into the two BMI subgroups; approximately half were normal weight ( $N = 61$ ) and half were overweight/obese ( $N = 57$ ). Mean birthweight was significantly different between the BMI groups ( $P = 0.02$ ). In addition, there were no significant differences in the rates of pregestational and/or gestational diabetes, hypertension or other chronic diseases between the strata.

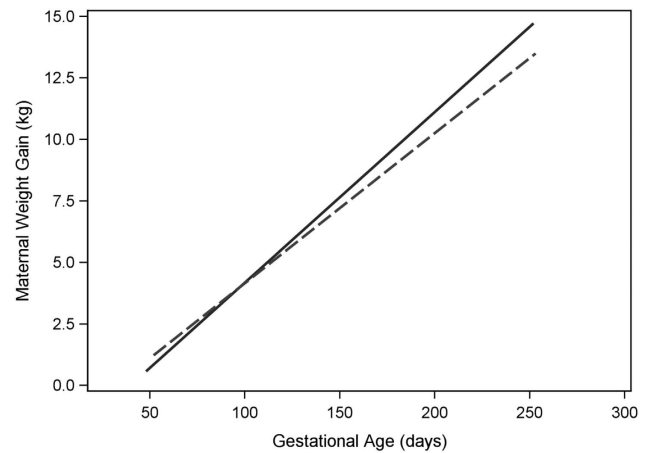
Figure 1 presents the cumulative maternal weight gain trajectories for both the normal weight and overweight/obese women in our sample. We found that the maternal weight progressively increased for both strata from 6 to 36 weeks gestation. However, the rate at which the maternal weight increased across gestation was significantly lower for overweight/obese women compared with their non-overweight counterparts ( $P < 0.05$ ).

Figures 2a and b contain the trajectories for preperitoneal fat thickness (pmax) and the subcutaneous fat thickness (smin) for both normal weight and overweight/obese women. Both smin and pmax were greater in overweight/obese women at all time points across gestation ( $P < 0.0001$  at each visit). However, pmax decreased across gestation in overweight/obese women, whereas it increased for normal weight women (Figure 2a); this difference in rate of change between groups was highly significant ( $P = 0.0003$ ). Thus, as gestation progressed, the mean difference

**Table 1.** Characteristics of the study sample

	Normal weight		Overweight/obese	
	N = 61	%	N = 57	%
<i>Race</i>				
White	50	82.0	47	82.5
Black	2	3.3	4	7.0
Asian	6	9.8	3	5.3
Other	3	4.9	3	5.3
<i>Hispanic ethnicity</i>				
Yes	2	3.3	4	7.0
No	59	96.7	53	93.0
<i>Maternal age</i>				
≤30	20	32.8	13	22.8
>30	41	67.2	44	77.2
<i>Prenatal smoking</i>				
Yes	7	11.5	4	7.0
No	51	83.6	51	89.5
Unknown	3	4.9	2	3.5
<i>Education level</i>				
College or less	30	49.2	36	63.2
Postgraduate	31	50.8	21	36.8
<i>Annual household income (US\$)</i>				
≤80 000	23	37.7	27	47.4
>80 000	33	54.1	28	49.1
Unknown	5	8.2	2	3.5
<i>Marital status</i>				
Married	55	90.2	51	89.5
Unmarried	6	9.8	6	10.5
<i>Parity</i>				
Primipara	26	42.6	15	26.3
Multipara	35	57.4	42	73.7
	<i>Mean</i>	<i>s.d.</i>	<i>Mean</i>	<i>s.d.</i>
Infant birth weight <sup>a</sup>	3276.4	492.0	3477.7	413.9

Abbreviation: s.d., standard deviation. <sup>a</sup>*P* = 0.02.



**Figure 1.** Maternal weight gain. The cumulative maternal weight gain (effective maternal weight at each study visit minus pre-pregnancy weight) trajectories for normal weight (solid line) and overweight/obese women (dashed line). Regression lines were calculated using a mixed linear regression model. The difference in rate of change between BMI strata is statistically significant (*P* < 0.05).

**COMMENT**

Obesity is characterized by distinct metabolic states that may ultimately be responsible for associated health problems. Growing evidence suggests that the regulation and effects of metabolic systems in overweight and obese individuals is substantially different from their normal weight counterparts during pregnancy.<sup>22–26</sup> Although differences in regional distribution of adipose tissue may have an important role in these metabolic differences, few studies have described how this distribution changes during pregnancy. Our study is among the first to document how the distribution of adipose tissue changes across pregnancy in overweight/obese women as compared with their normal weight counterparts.

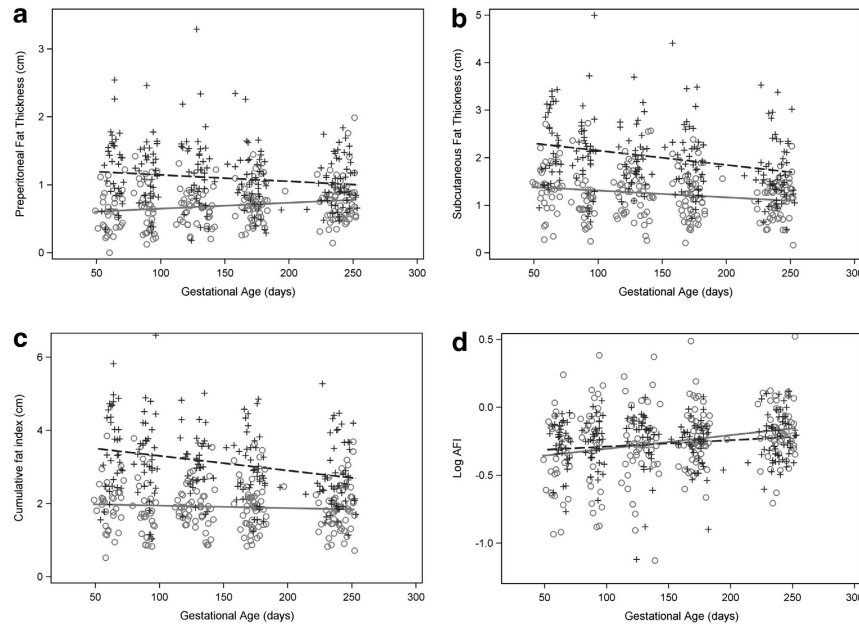
As expected, we found that overweight/obese women have larger anatomic depots of adipose tissue in all compartments. Although all women in our sample gain weight across pregnancy, overweight/obese women gain weight at a slower rate than their non-overweight counterparts, as frequently observed. However, our study reveals that this is accompanied by significant differences in the rates of change in ultrasound markers of adipose tissue distribution when comparing overweight/obese women with normal weight women.

Specifically, we find that there are significant differences in the accumulation of VAT between the two groups. Pregnancy is associated with the progressive deposition of VAT as suggested previously.<sup>17</sup> For normal weight women, smin decreases while pmax increases, resulting in little change in the cumulative fat index (smin plus pmax). However, the AFI becomes progressively larger with advancing gestation. These results suggest that abdominal adipose tissue is preferentially deposited in the visceral compartment as pregnancy progresses. For overweight/obese women smin, pmax and their sum all decrease across pregnancy. However, smin decreases more rapidly than pmax so that the AFI also increases with gestation in this stratum, albeit at a significantly lower rate than in normal weight women. As a result, the AFI in normal weight women is significantly larger than the overweight/obese group by the end of pregnancy.

Ultrasonographic measurement of the AFI is a surrogate marker of VAT that has been validated against abdominal computed tomography estimates and has been shown to be associated with metabolic markers such as insulin and circulating lipid levels in non-pregnant adults.<sup>16</sup> This index relies on measurement of the preperitoneal fat, which together with omental fat and

in pmax by obesity status decreased. In contrast, smin decreased across gestation in both BMI groups. As with pmax, although, the rate at which smin changed differed by BMI group (*P* = 0.01), with a slower rate of decline in overweight/obese women (Figure 2b).

The trajectories for the cumulative fat index (smin plus pmax) and the log-transformed AFI are plotted for both normal weight and overweight/obese women in Figures 2c and d. The sum of smin and pmax were greater in overweight/obese women at all time points across gestation; its value did not change across gestation in normal weight women, whereas it decreased for overweight/obese women (*P* = 0.0005; Figure 2c). The mean and standard deviation of log-transformed AFI measures by study visit in normal weight and overweight/obese women are presented in Table 2. The log AFI increased across gestation for both normal weight and overweight/obese women (Figure 2d). In cross-sectional analyses, there were no significant differences between normal weight and overweight/obese women at each study visit. However, in longitudinal analyses, the rate of change in the log AFI across gestation was greater for normal weight compared with overweight/obese women (*P* = 0.06; Figure 2d).



**Figure 2.** Maternal fat indices. Maternal abdominal fat thickness measures in normal weight (open circles) and overweight/obese (dashed line; crosses) women. Regression lines calculated using a mixed linear regression model are shown for normal weight women in blue and for overweight/obese women in red. *P*-values are provided for the significance of the difference in rate of change between BMI strata. (a) Preperitoneal fat thickness (pmax); *P* = 0.0003. (b) Subcutaneous fat thickness (smin); *P* = 0.01. (c) Cumulative fat index (smin + pmax); *P* = 0.0005. (d) Logarithm of the AFI; *P* = 0.06.

**Table 2.** Mean and s.d. of log-transformed AFI measures by study visit in normal weight and overweight/obese women

	Normal weight women		Overweight/obese women	
	Mean	+/-	Mean	+/-
Baseline	-0.37	0.27	-0.28	0.17
Visit 1	-0.26	0.32	-0.25	0.17
Visit 2	-0.28	0.28	-0.24	0.23
Visit 3	-0.22	0.21	-0.27	0.17
Visit 4	-0.17	0.21	-0.22	0.17

Abbreviations: AFI, abdominal fat index; s.d., standard deviation.

retroperitoneal fat is a component of visceral fat. These different visceral fat depots are thought to behave similarly and have very similar metabolic properties. Thus, in accordance with prior studies, we presume that the AFI is a good indicator of visceral fat.<sup>16,17</sup> However, these tissues may behave differently during pregnancy. It will ultimately be important to evaluate how this measure relates to various metabolic and inflammatory responses associated with adiposity during pregnancy.

In non-pregnant adults, it has been suggested that VAT deposition is associated with increased lipolysis and elevated free fatty acid flux through the portal system.<sup>7</sup> The exposure of both hepatic and extrahepatic tissues to free fatty acid may result in an abnormal insulin response, leading to insulin resistance and hypertriglyceridemia.<sup>27</sup> These changes mirror the maternal metabolic adaptations, including reduced insulin sensitivity, increased triglycerides, increased lipids and elevated leptin, that normally occur during the second and third trimesters of pregnancy.<sup>12,23,25</sup> Thus, the deposition of fat in the visceral compartment as pregnancy progresses is also likely to be a normal metabolic feature of pregnancy.

However, our results raise the possibility that differences in VAT deposition across pregnancy may be related to the different

metabolic adaptations to pregnancy seen in overweight and obese compared with lean women. We have recently shown that overweight/obese pregnant women do not have the same increases in leptin, total cholesterol and low-density lipoprotein cholesterol levels during pregnancy as their normal weight peers.<sup>23,25</sup> Similar to the pattern for pmax observed in this study, maternal leptin per body weight increased significantly across pregnancy for normal weight women, while decreasing significantly for overweight/obese women. These observations suggest potential relationships between adipose tissue distribution metabolic responses associated with the overweight/obese state that may be investigated in the future.

Maternal obesity is the outcome of a complex set of interactions among an array of genetic, biochemical and environmental factors that induce a pathogenic physiologic cascade that ultimately leads to adipose tissue dysfunction.<sup>28</sup> As such, the obese state cannot simply be characterized by simple anthropomorphic measurements such as BMI. Instead, the 'unhealthy obese' phenotype may be better characterized by visceral fat accumulation, specific metabolic and inflammatory responses of adipose tissue and their consequences on whole-body metabolism and energy utilization.<sup>11,28</sup> In non-pregnant adults, interindividual variation in body fat accretion (subcutaneous vs visceral) and the physiologic response to this body fat is one important factor associated with this phenotype and obesity-related morbidities.<sup>28</sup> Our results show that differences in anatomic distribution of adipose tissue may also be one factor that differentiates obese/overweight and lean women during pregnancy and are a step toward a more refined description of obese phenotype and its consequences during pregnancy. We expect that such a description will ultimately aid in identifying subgroups of obese individuals at substantially increased risk of adverse health outcomes who will most benefit from targeted interventions to prevent disease.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ACKNOWLEDGEMENTS

We thank Dr Dawn P Misra for critical reading of the manuscript. We gratefully acknowledge the infrastructure and personnel support of the University of Michigan Perinatal Assessment Center and the Michigan Clinical Research Unit. VKM was supported by a Doris Duke Clinical Scientist Development Award (Grant 2007092) and a NIH Mentored Scientist Award (K08-HD045609). The Michigan Clinical Research Unit is supported by a Clinical and Translational Science Award (UL1RR024986) from the National Institutes of Health. JKS was supported by a postdoctoral award from Wayne State University.

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