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

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INTRODUCTION

Maternal obesity is a major public health concern that is associated with poor outcomes for both the mother and the developing fetus.¹ 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.² 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.³,⁴ Crude metrics, such as body mass index (BMI), fail to acknowledge the many relationships among factors that give rise to this obese state.⁵ 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.⁶,⁷ 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 in its endocrine function, lipolytic activity and immunologic function.⁸,⁹ As a result, VAT has an important role in metabolic and inflammatory responses associated with adiposity.¹⁰ In non-pregnant adults, VAT deposition is associated with a greater risk of diabetes, dyslipidemia and accelerated atherosclerosis than SCAT accumulation.¹¹ 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.¹² A number of techniques for evaluating abdominal fat distribution have been developed.¹³ 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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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 kg m⁻²; N = 61) or overweight/obese (BMI ≥ 25 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.
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. 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. 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. 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 normal weight and overweight/obese women.16 Although AFI has been shown to be a good surrogate measure of VAT, studies with small sample sizes (N < 35) have started to document changes in AFI across pregnancy. 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, 14–18, 18–22 and 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 (BMI = kg/m²), and was categorized into two levels using World Health Organization (WHO) cutoff points as normal weight (≤ 25.0 kg m²) and overweight/obese (≥ 25.0 kg m²). 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.

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 kg m⁻²) and overweight/obese (≥ 25.0 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 gain 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 corrected by subtracting the estimated fetal weight, determined by ultrasound biometry using the method of Hadlock et al.20 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.16 Maternal subcutaneous (smin) and preperitoneal (pmax) fat were measured in triplicate at each study visit. Measurements were performed at the midline of the upper abdomen just below the xiphoid 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. 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%. Demographic and health-related characteristics of the study population were compared using χ² 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 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.
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 (across gestation in both BMI groups. As with pmax, although, in pmax by obesity status decreased. In contrast, smin decreased over overweight/obese women (AFI across gestation was greater for normal weight compared with overweight/obese women (Figure 2d). In cross-sectional analyses, there were no significant differences between normal weight and overweight/obese women (Figure 2c) at all 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).

### Table 1. Characteristics of the study sample

|                     | Normal weight | Overweight/obese |
|---------------------|---------------|------------------|
| N                   | 61            | 57               |
| Race                |               |                  |
| White               | 50            | 47               |
| Black               | 2             | 4                |
| Asian               | 6             | 3                |
| Other               | 3             | 3                |
| Hispanic ethnicity  |               |                  |
| Yes                 | 2             | 4                |
| No                  | 59            | 53               |
| Maternal age< 30    | 20            | 13               |
| > 30                | 41            | 44               |
| Prenatal smoking Yes| 7             | 4                |
| No                  | 51            | 51               |
| Unknown             | 3             | 2                |
| Education level     |               |                  |
| College or less     | 30            | 36               |
| Postgraduate        | 31            | 21               |
| Annual household income (US$) < 80000 | 23 | 27 |
| > 80000             | 33            | 28               |
| Unknown             | 5             | 2                |
| Marital status      |               |                  |
| Married             | 55            | 51               |
| Unmarried           | 6             | 6                |
| Parity              |               |                  |
| Primipara           | 26            | 15               |
| Multipara           | 35            | 42               |
| Infant birth weighta | 3276.4       | 492.0            |

Abbreviation: s.d., standard deviation. *P = 0.02.

**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. 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. 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. 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 computer tomography estimates and has been shown to be associated with metabolic markers such as insulin and circulating lipid levels in non-pregnant adults. This index relies on measurement of the preperitoneal fat, which together with omental fat and
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. 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. 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. 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. 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 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.

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**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                | 0.28                   |
| Visit 1             | 0.26                | 0.28                   |
| Visit 2             | 0.28                | 0.24                   |
| Visit 3             | 0.22                | 0.27                   |
| Visit 4             | 0.17                | 0.22                   |

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

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**Figure 2.** Maternal fat indices. Maternal abdominal fat thickness measures in normal weight (solid line; 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.
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