Energy Expenditure in Pregnant Women with Obesity Does Not Support Energy Intake Recommendations

Jasper Most1, Porsha M. Vallo1, L. Anne Gilmore1, Marshall St. Aman2,3, Daniel S. Hsia1, Abby D. Altazan1, Robbie A. Beyl1, Eric Ravussin1, and Leanne M. Redman4

Objective: This study aimed to identify factors that may predispose women to excess gestational weight gain (GWG).

Methods: Seventy-two healthy women with obesity (30 class I, 24 class II, 18 class III) expecting a singleton pregnancy were studied at 13 to 16 weeks gestation. Energy expenditure (EE) was measured during sleep (SleepEE, average EE from 0200-0500 hours) in a whole-room calorimeter, and total daily EE (TDEE) over 7 days using doubly labeled water. Glucose, insulin, thyroid hormones, and catecholamines were measured.

Results: Body composition explained 70% variability in SleepEE, and SleepEE accounted for 67% to 73% of TDEE. Though there was no evidence of consistent low metabolism, there was considerable variability. Low SleepEE was associated with insulin resistance and low triiodothyronine concentrations (both P < 0.01). Physical activity level was 1.47 ± 0.02. For women with SleepEE within 100 kcal/d of their predicted EE, TDEE was significantly less than the estimate (2,530 ± 91 vs. 2,939 kcal/d; P < 0.001) provided from the most recent gestational energy requirement model.

Conclusions: Pregnant women with obesity are inactive, possibly predisposing them to excess GWG. Current energy requirement models overestimate activity and may promote excess GWG in women with obesity. Furthermore, the observed large interindividual variability in basal metabolism may be important to consider when assessing the risk for excess GWG.

Introduction

According to the 2011-2014 National Health and Nutrition Examination Survey, 34.4% of reproductive-aged women (20-39 years) have obesity, which translates to approximately 1.4 million births every year from women with obesity in the United States (1). Alarmingly, the prevalence of obesity in women entering pregnancy is further increasing. Women with obesity are likely to have pregnancies complicated by excess gestational weight gain (GWG) (>60% prevalence) (2) and to have increased incidence of gestational diabetes, hypertensive disorders, nonelective cesarean section, and macromomonic infants (3).

Lifestyle modification interventions are now specifically targeting pregnant women with obesity with the goal to tilt energy balance toward better control of weight (and fat) gain and improvement of maternal and infant outcomes. The efficacy of randomized controlled trials designed to reduce GWG is, however, inconsistent, with modest mean effect sizes for weight gain attenuation, reduction of pregnancy complications, and detrimental infant health outcomes, including growth restriction, catch-up growth, and childhood adiposity (4,5). So far, the focus of such interventions has been based mostly on modification of diet and/or physical activity, similar to what has been done for obesity treatment in nonpregnant adults (6-8).

Understanding energy balance in early pregnancy may better guide the design of interventions that are appropriately tailored to pregnant women with obesity. The aim of this study was to combine stable isotopes and indirect calorimetry to characterize the components and determinants of energy expenditure (EE) and to assess energy requirements in early pregnancy in women with obesity. Measuring and understanding the components of EE in early pregnancy could...
lead to more effective lifestyle interventions to attenuate GWG and, thus, improve maternal and infant outcomes.

Methods

Study design
This study is part of a larger prospective observational study to assess the determinants of GWG in pregnant women with obesity (ClinicalTrials.gov identifier NCT01954342). Energy metabolism, including EE in sedentary and free-living conditions, substrate oxidation, physical activity, and endocrine mediators of energy metabolism were measured between 13 and 16 weeks of gestation in 72 pregnant women at Pennington Biomedical Research Center (Baton Rouge, Louisiana). The study was approved by the Pennington Biomedical Research Center Institutional Review Board, and all participants provided written informed consent prior to participation.

Participants and recruitment
Seventy-two women aged 18 to 40 years with obesity (BMI ≥ 30 kg/m²) at screening (<15 weeks of gestation) and a confirmed singleton, viable pregnancy were enrolled. Women were excluded for recent history of smoking, alcohol or drug use, preexisting hypertension (i.e., systolic blood pressure > 160 mmHg and diastolic blood pressure > 110 mmHg), diabetes (HbA1c ≥ 6.5%), human immunodeficiency virus or AIDS, severe anemia (hemoglobin < 8 g/dL and/or hematocrit < 24%), contraindications to magnetic resonance imaging (implanted metal objects, claustrophobia), prior or planned (within 1 year of expected delivery) bariatric surgery, or psychological or eating disorders. Furthermore, women using contraindicated medications or supplements that influence energy intake or expenditure, who planned to move out of the study area within the next 2 years or planned to be out of the study area for more than 4 weeks in the next 12 months, who planned termination, or who were unwilling to avoid pregnancy for 12 months following delivery were excluded. Study participants were recruited from January 2015 to January 2017 through community and social media advertisements and referrals by local obstetricians, as previously described (9).

Anthropometrics and body composition
At the screening visit (11 weeks ± 3 days), body height and weight were measured in a clinic gown to assess eligibility and classify obesity as class I (30 ≤ BMI < 35), class II (35 ≤ BMI < 40), or class III (BMI ≥ 40). At the study visit (14.7 ± 0.1 weeks), body weight was measured in the morning following an overnight fast with participants wearing a gown (gown weight was subtracted), and body composition was measured by air displacement plethysmography using BOD POD (COSMED USA, Inc., Concord, California) with women wearing provided spandex clothing. Thoracic gas volume was estimated by the software and corrected for a pregnancy-related decline of 100 mL (10). Body fat percentage was calculated per Siri (11), in which density of fat mass (FM) was 0.9 kg/L (12) and density of fat-free mass (FFM) was calculated based on gestational age using an exponential regression (13).

Total daily EE
Total daily EE (TDEE) was measured using doubly labeled water over 7 days (14). Briefly, participants provided two urine samples before being dosed (1.25 g of 10% enriched H218O and 0.10 g of 99.9% enriched 2H2O per kilogram) and subsequent urine samples at 4.5 hours, 12 hours, and days 6 and 7 after dosing. 18O and 2H abundance was measured by isotope ratio mass spectrometry (15). The CO2 production rate was calculated by using the equation of Schoeller et al. (14). Total body water was calculated as the average of total body water estimates by the dilution spaces of 18O and 2H (N0 and N1) using the 0 intercepts; N0/1.007 and N1/1.007*[N1/N0], in which N1/N0 is the dilution space ratio, calculated as the average of the group mean (1.0315 ± 0.0023) and each individual value (if N1/N0 ≥ 1, and if N1/N0 ≤ 1.07; n = 1 with N1/N0 ≤ 1), as previously described (16,17). TDEE was calculated by multiplying the CO2 production rate by the energy equivalent of CO2 for a respiratory quotient (RQ) of 0.866 (18), which reflects the mean 12-hour RQ of the cohort in pregnancy, as measured in the metabolic chamber, and a diet that provides approximately 50%, 30%, and 20% of energy from carbohydrate, fat, and protein, respectively. TDEE was not available for two participants because of missed urine collections or suspected misreporting of urine collection times.

Energy metabolism by metabolic chamber
Sleeping and resting EE (SleepEE and REE, respectively) were measured during an overnight stay in a metabolic chamber (19). Participants entered the chamber at 1830 hours after refraining from exercise, caffeine, and alcohol for the previous 36 hours. At 1900 hours, a standard dinner was served providing 30% of the estimated daily energy requirements (20) as 30% fat, 55% carbohydrate, and 15% protein. Lights were turned off between 2230 hours and 0600 hours the next morning. Beginning at approximately 0615 hours, after emptying of the bladder, REE was measured with the participant awake and lying supine on the bed for 30 minutes before exiting the chamber at 0700 hours. Oxygen consumption (VO2) (Siemens OXYMAT 6E, software v4.8.3; Siemens Industry, Inc., Bartlesville, Oklahoma) and carbon dioxide production (VCO2) (ABB Ursas26 AO2020, software v3.4.0; ABB Enterprises Software, Inc., Houston, Texas) were measured continuously. EE was calculated by using the Weir equation adjusted for urinary nitrogen excretion rate, which was measured during the chamber stay and extrapolated to 24 hours (21). The RQ was calculated as VCO2/VO2. Infrared sensors detected activity in the chambers (percent of minutes during which activity was detected). SleepEE is the mean EE between 0200 and 0500 hours (minutes when activity was <1%), extrapolated to 24 hours. REE is the mean of the last 20 minutes of the REE measurement, extrapolated to 24 hours. Metabolic flexibility, or the increase in postprandial RQ over fasting RQ, was calculated as the difference of the 4-hour postdinner RQ minus sleeping RQ. SleepEE and REE were not available for two and three participants, respectively, because of technical failure of the instrumentation.

Prediction of individual variability of EE
Linear regression was used to develop prediction equations for SleepEE and free-living conditions over 7 days (TDEE), using FFM and FM as independent variables. Age was not a significant predictor of EE and was therefore not included in the models. If EE is proportional to the metabolic mass, the EE predicted from the regression equation will be equal to the EE measured. The difference between the measured and predicted EE (called residual EE) allows for categorization of participants into the following three groups: those with an EE (kilocalories per day) that is significantly
higher than the regression line, which reflects high metabolism; those with an EE that is on the regression line, which reflects average metabolism; or those with an EE that is significantly lower than the regression line, which reflects low metabolism. For the present analysis, we used a previously published threshold of \( \pm 100 \text{ kcal/d} \) (22), which is a more conservative estimate compared with using tertiles (23).

### Physical activity

Physical activity was estimated from TDEE and REE by using three different calculations. First, activity-related EE (AREE) was calculated in absolute terms as the remaining EE from 0.9 \( * \text{TDEE} - \text{REE} \), which assumes diet-induced thermogenesis as 0.1 \( * \text{TDEE} \). Second, physical activity level (PAL) was calculated as \( \text{PAL} = \text{TDEE}/\text{REE} \) (24). Third, because of the inherent problem of using ratios when the two variables have an intercept not equal to zero, we expressed physical activity as residual AREE. Residual AREE is calculated as measured TDEE minus TDEE predicted using regression, with TDEE as a dependent variable and SleepEE as an independent variable (25). This value is positive for subjects with higher physical activity than average and is negative for subjects with lower physical activity than average, independent of metabolic body size. Because residual AREE is adjusted for metabolic body size (SleepEE), this value is directly proportional to the amount of physical activity. In addition, physical activity was assessed over 24 hours, including the chamber stay, by using a SenseWear Armband accelerometer (Model MF-SW, BodyMedia Inc., Pittsburgh, Pennsylvania).

### Clinical chemistry

Urinary nitrogen, creatinine, norepinephrine, and epinephrine were measured by enzyme-linked immunosorbent assay (ELISA) in an overnight pooled urine sample collected during the chamber stay (Bio-Rad microplate reader; DLD Diagnostika, Hamburg, Germany). A fasting blood sample was collected after exiting the chamber for measurement of insulin, triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (IMMULITE 2000; Siemens, Broussard, Louisiana), and glucose (DXC600; Beckman Coulter Inc., Brea, California).

### Fetus

Medical record data pertaining to the pregnancy was obtained before study enrollment and at the end of pregnancy to confirm gestational age and fetal sex. Fetal weight in early pregnancy was estimated using two-dimensional ultrasound assessments of head circumference, biparietal diameter, abdominal circumference, and femoral length (26) obtained by the same sonographer.

### Statistics

All analyses were carried out by using SAS/STAT software, version 9.4 of the SAS System for Windows (SAS Institute, Inc., Cary, North Carolina). All tests were evaluated by using significance level \( \alpha = 0.05 \). To test for differences between obesity classes, linear models were produced to obtain estimates used in \( F \) tests and two-sample \( t \) tests for continuous variables, and \( \chi^2 \) tests were performed for categorical variables. Post hoc testing was used for pair-wise comparisons. Data is expressed as means \( \pm \) SEM derived from the linear models.

### Results

#### Participant characteristics

Enrolled women (\( N = 72; \) Table 1) were 27 \( \pm 0.6 \) years old, and 53% had at least one previous live birth. By design, the women all were classified as having obesity but were healthy as

| Variable | Overall, \( N = 72 \) | Class I, \( n = 30 \) | Class II, \( n = 24 \) | Class III, \( n = 18 \) | \( P \) for obesity class |
|-----------|-----------------------|-------------------|-------------------|-------------------|------------------------|
| GA at visit in weeks/days | 14 4/7 ± 1/7 | 14 4/7 ± 1/7 | 14 5/7 ± 1/7 | 14 4/7 ± 1/7 | 0.88 |
| GWG, 1st trimester, g/wk | 118 ± 21 | 125 ± 24 | 99 ± 36 | 129 ± 43 | 0.83 |
| Age, y | 27.7 ± 0.6 | 27.3 ± 1.0 | 27.0 ± 0.9 | 29.4 ± 1.2 | 0.24 |
| Race (W, B, O), n | 32, 34, 6 | 16, 13, 1 | 11, 11, 2 | 5, 10, 3 | 0.35 |
| BMI, kg/m² | 37.1 ± 0.7 | 32.3 ± 0.3 | 37.0 ± 0.3 | 45.2 ± 1.1 | |
| FFM, kg | 54.2 ± 1.0 | 50.4 ± 1.1 | 54.0 ± 1.5 | 60.7 ± 2.1 | <0.001 |
| FM, kg | 45.9 ± 1.5 | 36.8 ± 1.0 | 44.8 ± 1.1 | 62.7 ± 2.9 | <0.001 |
| FM, % | 45.4 ± 0.6 | 42.2 ± 0.7 | 45.4 ± 0.8 | 50.6 ± 1.2 | <0.001 |
| HbA₁c, % | 5.4 ± 0.04 | 5.4 ± 0.1 | 5.3 ± 0.1 | 5.6 ± 0.1 | 0.12 |
| Glucose, mg/dL | 89 ± 1 | 88 ± 1 | 87 ± 2 | 92 ± 2 | 0.09 |
| Insulin, IU/mL | 15.6 ± 1.0 | 12.3 ± 1.0 | 13.8 ± 1.6 | 23.6 ± 1.8 | <0.001 |
| Systolic BP, mmHg | 108 ± 1 | 106 ± 2 | 107 ± 2 | 112 ± 2 | 0.07 |
| Diastolic BP, mmHg | 67 ± 1 | 65 ± 1 | 66 ± 1 | 71 ± 2 | 0.01 |
| Parity (0, 1, 2+, n | 34, 22, 16 | 12, 8, 10 | 14, 8, 2 | 8, 6, 4 | 0.29 |
| Infant sex M, F, n | 33, 36 | 15, 14 | 11, 12 | 7, 10 | 0.79 |

Data expressed as means \( \pm \) SEM. Differences in participant characteristics tested with linear models. GA, gestational age; GWG, gestational weight gain; W/B/O, white, black or African American, other; FFM, fat-free mass; FM, fat mass; HbA₁c, hemoglobin A₁c; BP, blood pressure; M, male; F, female.
Figure 1 Correlations between (A) fat-free mass, (C) sleeping energy expenditure (SleepEE), and (E) total daily energy expenditure (EE). (B) Residuals for total daily energy expenditure (TDEE), (D) SleepEE, and (F) activity-related EE (AREE) by obesity class. Each data point represents one participant. For residual SleepEE, -100 kcal/d and 100 kcal/d are used to identify low and high metabolism.

TABLE 2 Energy expenditure in pregnant women with obesity

| Variable    | Overall, N = 72 | Class I, n = 30 | Class II, n = 24 | Class III, n = 18 | P for obesity class |
|-------------|-----------------|-----------------|------------------|-------------------|---------------------|
| TDEE, kcal/d | 2,639 ± 46      | 2,540 ± 57      | 2,623 ± 86       | 2,847 ± 99        | 0.03                |
| SleepEE, kcal/d | 1,768 ± 33     | 1,621 ± 29      | 1,724 ± 47       | 2,053 ± 62        | <0.001              |
| REE, kcal/d  | 1,825 ± 34      | 1,686 ± 39      | 1,775 ± 50       | 2,102 ± 58        | <0.001              |
| AREE, kcal/d | 569 ± 30        | 596 ± 47        | 585 ± 56         | 499 ± 50          | 0.43                |
| PAL         | 1.47 ± 0.02     | 1.51 ± 0.04     | 1.48 ± 0.04      | 1.38 ± 0.02       | 0.04                |

Data expressed as means ± SEM. Energy expenditure measured between 13 and 16 weeks of gestation. Differences in energy by obesity class were tested with linear models.
EE, energy expenditure; TDEE, total daily EE; SleepEE, sleeping EE; REE, resting EE; PAL, physical activity level; AREE, activity-related EE.
confirmed by normal glucose tolerance and blood pressure. First trimester body weight measured at approximately 11 weeks and 3 days classified 42% of participants with class I obesity (30/72), 33% with class II (24/72), and 25% with class III (18/72). Across obesity classes, participants were similar with respect to age, race, fasting glucose, parity, and infant sex. As expected, FM was proportional to obesity ($P < 0.001$), and FFM was higher with class III compared with class II and class I but not different between class I and class II. Diastolic blood pressure and insulin were the only metabolic parameters that were significantly different between obesity classes.

**TDEE**

In early pregnancy, TDEE was $2,639 \pm 46$ kcal/d (Table 2). TDEE positively correlated with weight ($r = 0.46; P < 0.001$), FFM ($r = 0.57; P < 0.001$; Figure 1A), and FM ($r = 0.32; P < 0.01$). The following are the prediction equations for relating TDEE to FFM and FM as well as to weight: 

- $\text{TDEE}_{\text{predicted}}[\text{kcal/d}] = 1,081 + [26.5\times\text{FFM}, \text{kg}] + [3.1\times\text{FM}, \text{kg}]$,
- $R^2 = 0.33$, $P < 0.001$
- and $\text{TDEE}_{\text{predicted}}[\text{kcal/d}] = 1,507 + [11.5\times\text{weight}, \text{kg}]$, $R^2 = 0.21$, $P < 0.001$.

**Sedentary EE (SleepEE and REE)**

In early pregnancy, SleepEE was $1,768 \pm 33$ kcal/d, with a high degree of variability among pregnant women ($n = 70$; Figure 1C). As expected, SleepEE in early pregnancy correlated with weight ($r = 0.79; P < 0.001$), FFM ($r = 0.77; P < 0.001$; Figure 1C), and FM ($r = 0.68; P < 0.01$).

The following are the prediction equations for relating SleepEE to FFM and FM as well as to weight: 

- $\text{SleepEE}_{\text{predicted}}[\text{kcal/d}] = 388 + [19.0\times\text{FFM}, \text{kg}] + [7.6\times\text{FM}, \text{kg}]$, $R^2 = 0.69$, $P < 0.001$
- and $\text{SleepEE}_{\text{predicted}}[\text{kcal/d}] = 588 + [11.8\times\text{weight}, \text{kg}]$, $R^2 = 0.62$, $P < 0.001$. Findings were similar for REE ($n = 69$; Table 2). The following are the prediction equations for relating REE to FFM and FM as well as to weight: 

- $\text{REE}_{\text{predicted}}[\text{kcal/d}] = 368 + [20.7\times\text{FFM}, \text{kg}] + [7.2\times\text{FM}, \text{kg}]$, $R^2 = 0.68$, $P < 0.001$
- and $\text{REE}_{\text{predicted}}[\text{kcal/d}] = 604 + [12.1\times\text{weight}, \text{kg}]$, $R^2 = 0.61$, $P < 0.001$.

**Physical activity**

The energy expended during activity (AREE) was not proportional to body mass and was not different between obesity classes (Table 2). According to the *Physical Activity Guidelines for Americans* (27), 88% (59/67) of the participants were sedentary (PAL $< 1.7$), 12% (8/67) were moderately active (1.7 $\leq$ PAL $< 2.0$), and no participant was highly active (PAL $\geq 2.0$). The average PAL was 1.47 $\pm$ 0.02, and PAL was lowest in women with class III obesity compared with women with class I and II ($P = 0.01$ and $P = 0.06$, respectively; Table 2). Physical activity expressed as residual AREE (TDEE adjusted for SleepEE, TDEE $[\text{kcal/d}] = 618 + [1.154\times\text{SleepEE}, \text{kcal/d}]$, $R^2 = 0.59$, $P < 0.001$) was not statistically different between obesity classes ($P = 0.14$; Figure 1E–1F). Reduced physical activity with higher obesity class was confirmed by the accelerometer and the time spent in various intensities of physical activity. Women with class III spent significantly less time in moderate or vigorous activities than women with class I and II (I: 243 $\pm$ 62 min/wk, II: 102 $\pm$ 15 min/wk, and III: 86 $\pm$ 1 min/wk; $P = 0.02$), and consequently, the average metabolic equivalents per day were also significantly lower ($P < 0.001$).

**Components of EE**

The primary constituent of TDEE in early pregnancy was SleepEE, accounting for 67% $\pm$ 1%. Estimating diet-induced thermogenesis as 10% of TDEE for all subjects, 3.0% $\pm$ 4% of TDEE was attributed to the energy cost of arousal (not significant between obesity classes). The remaining component of TDEE was AREE (22% $\pm$ 1%), which is the energy cost of structured exercise and activities of daily living or nonexercise activity thermogenesis.

**Endocrine mediators of EE**

Fasting concentrations of T3 were significantly higher in women with class III obesity compared with class I and II (214 $\pm$ 11 ng/dL vs. 173 $\pm$ 7 ng/dL and 174 $\pm$ 8 ng/dL, respectively; $P = 0.002$ and $P = 0.003$). T4 and thyroid stimulating hormone were not different between obesity classes. EE (TDEE, SleepEE, and REE) correlated with T3 (Figure 2A) but not with urinary catecholamine excretion. Furthermore, fasting glucose, insulin, and homeostatic model assessment of insulin resistance were also positively correlated with EE activities.
Metabolic status

By using the linear regression models TDEE and SleepEE derived from the whole cohort, we predicted EE for each participant based on FFM and FM in early pregnancy. There was a large degree of variability observed among the participants for the residual EE of TDEE (Figure 1B) and SleepEE (Figure 1D). Residual EE was not significantly different between obesity classes \( (P = 0.41) \). When applying a published threshold of \( \pm 100 \) kcal/d to SleepEE \( (22) \), approximately 50% of women had a metabolic rate commensurate with their respective metabolic mass. However, 27\% (19/70) had a residual EE \( \leq -100 \) kcal/d, which could be considered low metabolic rate, and 24\% (17/70) had a residual EE \( 
\geq 100 \) kcal/d, which could be considered high metabolic rate.

Irrespective of obesity class, the subgroup with high SleepEE had higher fasting glucose \( (94 \pm 3 \text{ vs. } 85 \pm 1 \text{ mg/dL}; \ P = 0.003) \), insulin \( (18.9 \pm 2.2 \text{ vs. } 11.5 \pm 1.5 \text{ IU/mL}; \ P = 0.007) \), and T3 concentrations \( (214 \pm 9 \text{ vs. } 168 \pm 9 \text{ ng/dL}; \ P = 0.001) \) compared with the subgroup with low SleepEE. There was no difference in the distribution of infant sex between the women with low metabolic rate (8 girls, 9 boys) and high metabolic rate (5 girls, 12 boys; \( P = 0.29) \). These results are robust against the use of other thresholds for high versus low EE (e.g., tertiles > 48 kcal/d and < -65 kcal/d, both \( n = 23 \); or 10\% of SleepEE > 212 kcal/d and < -186 kcal/d, both \( n = 9 \)).

Substrate oxidation

The average RQs during the total overnight stay and during sleep (0200-0500 hours) were 0.875 \pm 0.004 and 0.854 \pm 0.005, respectively, and were not different between obesity classes. Thus, there was no difference in the overnight oxidation rates for fat and carbohydrates. Moreover, metabolic flexibility in response to the standardized dinner was also comparable between obesity classes (overall, 0.042 \pm 0.003).

Energy requirements

In the 49\% of women with energy metabolism within 100 kcal/d of the predicted EE \( (n = 13, 12, \text{ and } 9 \text{ with class I, II and III obesity, respectively}) \), the mean TDEE was 2,530 \pm 91 kcal/d \( (\text{PAL} = 1.46 \pm 0.09) \). To sustain weight gain within the Institute of Medicine (IOM) guidelines (170-270 g/wk) from week 13 until delivery \( (28) \), between 2,754 and 2,835 kcal/d is required. Using the most recent model to estimate maternal TDEE \( (20) \), TDEE was calculated to be 2,939 kcal/d \( (P = 0.001 \text{ vs. measured TDEE}) \), with 3,163 to 3,245 kcal/d necessary to promote appropriate GWG.

Discussion

GWG above the 2009 recommendations by the IOM is most prevalent among women with obesity. In this study, we successfully measured the different components of daily EE during early pregnancy (\(~15\) weeks) and assessed the physiological determinants of EE during pregnancy in women with obesity. Our major goal was to determine energy requirements during early pregnancy and to identify potential risk factors for excess GWG that could be targeted for intervention strategies. Studies have seldom measured EE in early gestation, and none has phenotyped metabolism in this manner in women with obesity \( (29-34) \). In 72 pregnant women with obesity, we found that TDEE in early pregnancy was highly variable but was positively correlated with metabolic mass, systemic thyroid hormone concentration, and insulin resistance. Importantly, the calculated AREE made up only 20\% of TEE, which is low compared with other reports \( (29,33,35,36) \). Furthermore, while there was no evidence for low EE in this cohort of women with obesity, at the individual level, approximately one-third of women had evidence of low metabolic rate (measured EE \( < -100 \) kcal/d than predicted EE), which may predispose them to excess GWG. In the women with energy metabolism proportional to their metabolic mass, this study estimates that the energy requirement needed to maintain weight gain within the IOM guidelines is between \(~2,760\) and \(~2,840\) kcal/d. Alarming, this estimate is significantly less than the individual estimate that would be derived with a currently applied model \( (3,160-3,240 \text{ kcal/d}) \) \( (20) \). Possible causes for the high prevalence of excess GWG among women with obesity are likely multifactorial. First, low levels of physical activity reduce overall TDEE and therefore favor positive energy balance. Second, a low EE for a given metabolic mass has been shown to increase risk for weight gain in nonpregnant individuals \( (23,37) \) and in pregnant women \( (38,39) \). Third, weight gain could be the result of a particular metabolic phenotype that includes impaired fat oxidation, low thyroid function, and low sympathetic nervous system activity \( (40) \). Lastly, GWG could simply be the result of energy intake exceeding energy requirements. Thus, both behavior and physiology are important considerations when identifying risk factors for excess GWG in pregnancy.

In this cohort of pregnant women with obesity, TDEE was primarily composed of sedentary EE \( (70\%), \text{ i.e., resting and sleeping. Assuming diet-induced thermogenesis accounted for 10\% of TDEE, physical activity contributed to TDEE only in very small quantities. Leaner women seemed to spend a smaller portion (\(~60\%) \) of their TDEE in sedentary conditions in early pregnancy and therefore were more active, as has been reported in other studies \( (29-33) \). In line with these findings, PAL was low among our cohort of women with obesity and more so in those with class III obesity, compared with women without obesity \( (29,33,35,36) \). By using accelerometers, we confirmed that pregnant women with obesity maintained a very sedentary lifestyle in early pregnancy. Strikingly, women with class II and III failed to engage in moderate physical activity for the recommended 150 min/wk almost exclusively \( (83\% \text{ and } 94\% \text{ with class II and III, respectively}) \) \( (27,41,42) \). The benefits of physical activity during pregnancy are well described \( (42) \). Physical activity during pregnancy may reduce the likelihood for pregnancy complications and may improve infant health outcomes, such as infant birth weight and abdominal circumference \( (5) \). Therefore, in line with the American College of Obstetricians and Gynecologists \( (42) \), our data suggests that there is an opportunity to position public health messages on maintaining physical activity throughout pregnancy with an emphasis toward women with obesity.

After correction for body mass, we found no difference in REE between obesity classes or when this cohort was compared with a
group of women without obesity in early pregnancy (29,43). Although REE may not be physiologically high or low in women with obesity overall, we found evidence for both low and high metabolic rates of up to ±17% of SleepEE (and REE) among our cohort (±350 kcal/d). This variability is comparable to studies in both nonpregnant and pregnant individuals and thus is not specific to obesity (23,29). Given the close relationship between metabolism and body-weight regulation (40), the observation of low EE in some women with obesity in early pregnancy may have clinical relevance to GWG. Having low EE is believed to be a homeostatic mechanism activated when energy balance is manipulated to defend body mass and favor weight gain (22). While GWG data is not yet available, the low metabolic rate was supported by lower concentrations of thyroid hormone and insulin. Indeed, in nonpregnant individuals, both low thyroid hormone level and reduced insulin sensitivity are considered to be metabolic mediators of weight gain (40). Interestingly, other metabolic mediators that also predict weight gain, such as low sympathetic nervous system activity and low rates of fat oxidation, were not observed in the subgroup with low metabolic rate. Future studies should further investigate the role of endocrine mediators of energy balance throughout pregnancy and in relation to GWG in obesity.

To guide pregnant women toward healthy GWG, studies have been conducted to determine trimester-specific energy requirements. In 2009, data from the classic study by Butte et al. was used to develop a maternal energy requirement model (20). This model, validated against two independent cohorts of pregnant women (31,32), uses individual age, height, body weight, and GWG to make assumptions regarding individual body composition and physical activity and to estimate trimester-specific energy requirements (20). Using this model, EE is significantly higher than measured TDEE for women in our cohort. The data used in the development and validation of this published energy requirement model was composed primarily of women without obesity, and the reference cohort included only three women with pregravid obesity (20). According to a secondary analysis we performed on this data, all three women with obesity gained in excess of the 2009 IOM guidelines (43). Our study is the largest to metabolically phenotype a cohort of pregnant women with obesity and raises the question of whether the assumptions for maternal EE, specifically physical activity, may significantly overestimate the energy requirement for women with obesity. Specifically, the PAL of pregnant women in the model (i.e., 1.7) is higher than what we observed in pregnant women with obesity overall (1.5) and substantially higher than for women with class III obesity (1.4). Therefore, although this energy requirement model has been validated, albeit in cohorts without obesity, it does not appear to be valid for women with obesity. Moreover, caution should be used when applying estimates from this model to pregnant women with obesity to guide weight-gain treatment.

In conclusion, this is the first cross-sectional study to precisely measure the different components of EE in pregnant women with obesity. Given that maternal obesity is a risk factor for excess GWG and adverse pregnancy outcomes, characterization of energy balance with an overarching aim to define energy requirements and to identify components and determinants of EE could inform the development of future targeted intervention approaches. Our study, combining stable isotopes, indirect calorimetry, accelerometry, and body composition assessments, suggests that an increased risk for excess GWG among women with obesity may be driven by low physical activity present in early pregnancy. In addition, our data also suggests that metabolic impairments may be implicated in about 30% of cases (conservatively defined as residual SleepEE < -100 kcal/d). Our findings point to the need for interventions to promote healthy weight gain and to ameliorate obesity-induced pregnancy risk factors by targeting low physical activity, which is evident from the start of pregnancy. Physical activity likely benefits the mother and fetus and positively contributes to healthy maintenance of energy balance throughout gestation. Finally, this work identifies that currently utilized energy intake recommendations are likely overestimating the energy requirements of pregnant women with obesity, and therefore it is imperative that current energy intake recommendations are expanded to include women with maternal obesity. Future studies investigating the mechanisms of GWG in women with obesity and the relevance of metabolism early in pregnancy are needed.

Acknowledgments

We would like to acknowledge the technical assistance of Jennifer Rood, Loren E. Cain, Kimberly Landry, and Brian Gilmore; administrative support from Elizabeth F. Sutton, Kelsey Olson, Alexandra Beyer, Alexis O’Connell, and Natalie Comardelle; and recruitment and retention support from Ralph Dauterive, Evelyn Griffin, and Evelyn Hayes. Above all, we thank the participants for allowing us to follow their pregnancies.

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