Dynamic energy-balance model predicting gestational weight gain

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ABSTRACT

Background: Gestational weight gains (GWGs) that exceed the 2009 Institute of Medicine recommended ranges increase risk of long-term postpartum weight retention; conversely, GWGs within the recommended ranges are more likely to result in positive maternal and fetal outcomes. Despite this evidence, recent epidemiologic studies have shown that the majority of pregnant women gain outside the target GWG ranges. A mathematical model that predicts GWG and energy intake could provide a clinical tool for setting precise goals during early pregnancy and continuous objective feedback throughout pregnancy.

Objective: The purpose of this study was to develop and validate a differential equation model for energy balance during pregnancy that predicts GWG that results from changes in energy intakes.

Design: A set of prepregnancy BMI–dependent mathematical models that predict GWG were developed by using data from a longitudinal study that measured gestational changes in fat-free mass, fat mass, total body water, and total energy expenditure in 63 subjects.

Results: Mathematical models developed for women with low, normal, and high prepregnancy BMI were shown to fit the original data. In 2 independent studies used for validation, model predictions of fat-free mass, fat mass, and total body water matched actual measurements within 1 kg.

Conclusions: Our energy-balance model provides plausible predictions of GWG that results from changes in energy intakes. Because the model was implemented as a Web-based applet, it can be widely used by pregnant women and their health care providers. Am J Clin Nutr 2012;95:115–22.

INTRODUCTION

Greater than 60% of women of childbearing age in the United States are currently classified as overweight or obese [BMI (in kg/m²) ≥25] (1). Moreover, >5% of overweight and obese women exceed the 2009 IOM1 recommendations for GWG (1–3). A growing body of evidence indicates that both high prepregnancy BMI and GWGs that exceed the recommended ranges increase risk of long-term postpartum weight retention; conversely, GWGs within the recommended ranges are more likely to result in positive maternal and fetal outcomes (5–9).

To support the 2009 recommended GWG targets, the IOM committee (3) suggested that “interventions will be needed to assist women, particularly those who are overweight or obese at the time of conception, in meeting the new GWG guidelines.” To meet this need, the IOM report recommended that health care providers set GWG goals during early pregnancy, monitor GWG, and provide nutritional counseling with pregnant women. A mathematical model that predicts the impact of changes in dietary energy intake on GWG could be a useful tool for setting goals and providing continuous objective feedback during pregnancy.

The modeling approach presented in this article adopted established methods for the construction of dynamic weight-change prediction models in nonpregnant adults (10–19). Dynamic models of weight change originate from the first law of thermodynamics that dictates that changes in energy storage within the body must be equal to the energy intake minus the TEE (20).

In the current article, we developed a dynamic mathematical model that predicts GWG and dietary energy intake by using a comprehensive database on pregnancy-related changes in energy balance (3, 21–26). Model simulations were conducted by using differential equations to test whether simulated curves generated physiologically plausible results. Last, the final models were validated against longitudinal observations in pregnant women. Our mathematical model provides a useful clinical tool to predict GWG from changes in maternal dietary energy intake.

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4 Abbreviations used: FFM, fat-free mass; FM, fat mass; GWG, gestational weight gain; IOM, Institute of Medicine; TBP, total body protein; TBW, total body water; TEE, total energy expenditure.

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METHODS

Overview of model development and validation

Our dynamic mathematical model of weight changes during pregnancy reduces to the energy-balance equation (20) as follows:

\[ \text{ES} = \text{EI} - \text{TEE} \quad (1) \]

where ES denotes the rate of energy stored in kilocalories per day, EI represents the rate of energy intake in kilocalories per day, and TEE is the rate of total energy expended in kilocalories per day. The term ES was constructed as a sum of the instantaneous rates of change of different energy storage compartments, and the term TEE was developed from doubly labeled water measurements. A differential equation was used to describe ES from changes in body composition, specifically the FFM and FM components. The resulting solution of the differential equation predicts body weight as a function of time. The EI parameter can be altered to observe how variations in energy intake affect body weight.

The model development required a sufficiently large database of accurately measured measurements of body composition, TEE, and total body mass before conception and during pregnancy. ES was estimated from changes in body composition during pregnancy. The measurement of body composition is challenging during pregnancy because some methods such as dual-energy X-ray absorptiometry are not safe for application during pregnancy, and other methods assume physiologic constants that are not valid during pregnancy. As a result, multicomponent body-composition models were used that entailed measurements of several body compartments. For model building, we used a comprehensive longitudinal pregnancy study of Butte et al (24, 25) that collected all required body-composition and energy-expenditure measurements with a sufficient number of subjects.

The model validation required individual subject data with accurate measurements of pregravid weight. Maternal recall of prepregnancy weight is not always reliable (3); however, studies that measure pregravid weight are rare because recruitment before conception is logistically challenging (3). For model validation, the following 2 independent pregnancy studies were identified with conception is logistically challenging (3). For model validation, the 12 subjects in the Goldberg study (22) were healthy nonsmokers with one exception. Prepregnancy BMI averaged 23.0 ± 3.3. TBW was determined before pregnancy and every 6 wk during pregnancy by using deuterium dilution as part of the doubly labeled water method for TEE. FM and FFM were calculated from TBW measurements by using pregnancy-specific hydration constants (22).

The 10 subjects in the Kopp-Hoolihan study (23) were healthy nonsmokers. Prepregnancy BMI averaged 23.1 ± 2.1. TBW was determined before pregnancy and between gestational weeks 8–10, 24–26, and 34–36 by using deuterium dilution as part of the doubly labeled water method for TEE. FM and FFM were calculated from TBW measurements and the Siri 4-compartment model on the basis of densitometry, deuterium dilution, and pregravid bone mineral content. Subject baseline demographic and TEE data are shown in Table 1.

Model development

To introduce our mathematical approach, we begin with a general overview of model construction. The terms of the energy-balance equation (Equation 1), ES, EI, and TEE were developed by separating maternal weight, expressed in kilograms, into 2 compartments, FFM and FM. The sum of maternal FFM and FM represented body weight (W) as

\[ W = \text{FFM} + \text{FM} \quad (2) \]

Subjects

The model development relied on the use of body composition and TEE measurements made concurrently in 63 women before pregnancy and at weeks 9, 22, and 36 of pregnancy (24, 25). In this study, subject data were separated into 3 BMI groups of low BMI (≤19.8), normal BMI (19.8–26), or high BMI (≥26), which were based on the BMI classifications of the 1990 IOM guidelines (3). We accordingly developed 3 separate models of GWG for the 3 pre gravid BMI groups.

Body composition was measured by using a 4-compartment body-composition model before conception and during gestation (weeks 9, 22, and 36). The 4-compartment model included measurements of total body weight, TBW from deuterium dilution, total body volume from underwater weighing, and bone-mineral content from dual-energy X-ray absorptiometry scans taken before pregnancy. TBW was estimated from serial measurements of total body potassium. TEE was determined by the doubly labeled water method at preconception and weeks 22 and 36 of gestation.

The model was validated by using 2 independent study databases that included pregravid measurements (22, 23). The 12 subjects in the Goldberg study (22) were healthy nonsmokers with one exception. Prepregnancy BMI averaged 23.0 ± 3.3. TBW was determined before pregnancy and every 6 wk during pregnancy by using deuterium dilution as part of the doubly labeled water method for TEE. FM and FFM were calculated from TBW measurements by using pregnancy-specific hydration constants (22).

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### Table 1

<table>
<thead>
<tr>
<th>Database</th>
<th>n</th>
<th>Age (y)</th>
<th>Height (cm)</th>
<th>Pregravid weight (kg)</th>
<th>GWG (kg)</th>
<th>Baseline TEE (kcal/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butte et al (24, 25)</td>
<td>63</td>
<td>30.6 ± 4.2*</td>
<td>163.7 ± 5.8</td>
<td>60.2 ± 11.3</td>
<td>15.0 ± 3.8</td>
<td>2495.2 ± 404.7</td>
</tr>
<tr>
<td>Goldberg et al (22)</td>
<td>12</td>
<td>28.8 ± 3.3</td>
<td>164.0 ± 7.0</td>
<td>61.7 ± 8.8</td>
<td>14.5 ± 4.5</td>
<td>2273.6 ± 346.3</td>
</tr>
<tr>
<td>Kopp-Hoolihan et al (23)</td>
<td>10</td>
<td>29.1 ± 5.0</td>
<td>163.0 ± 17.8</td>
<td>64.8 ± 7.8</td>
<td>17.9 ± 5.4</td>
<td>—</td>
</tr>
</tbody>
</table>

1 GWG, gestational weight gain; TEE, total energy expenditure.
2 Mean ± SD (all such values)
3 Did not report the group mean TEE.
4 Individual baseline height was not reported in the Kopp-Hoolihan study (23). Model simulations required height, and therefore, the average height was estimated by assuming a national average height of 163.0 cm (27).

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During pregnancy, this sum included all maternal and fetal tissues. Instead of developing a system of 2 coupled differential...
equations with state variables FFM and FM, we algebraically related FFM to FM by using longitudinal study data (24, 25). This algebraic relation could be formulated from reported relations between changed FFM and gestational weight (24, 25) which indicated that ΔFFM was a linear function of gestational weight.

The first FFM-function formulation step required knowledge of how FFM changes during pregnancy in relation to weight. The major change in FFM from the pregravid state comes from the growth of fetal and placental tissues and expansion of the uterus, mammary glands, blood, and extracellular fluid (28), which can be captured by quantifying changes in TBW and TBP. Therefore, a precursor to FFM-function development required construction of TBW and TBP gestational weight functions.

**TBW**

Maternal TBW has been linearly related to GWG (24–26). We applied the longitudinal data for the low-, normal-, and high-BMI categories (24, 25) to fit a linear TBW function to simultaneously measured gestational weight. TBW functions for each BMI category are presented in Table 2.

**TBP**

Similar to the TBW weight-dependent function, TBP was shown to correlate with gestational weight for each BMI category (24, 25). In the longitudinal study (24, 25), TBP decreased in the first trimester and increased thereafter, which suggested a cubic relation to gestational weight. For mathematical and computational tractability, we modeled TBP as a piecewise linear equation. We denote the dependence of TBP on weight by subscripting with W. For example, the low-BMI category piecewise linear model is

$$\text{TBP}_W = -0.005 W + 9.3 \text{ if } W \leq 52 \text{ kg, } 0.1 W + 1.3 \text{ if } 52 < W \leq 57.7 \text{ kg, and } 0.08 W + 3.1 \text{ if } W > 57.7 \text{ kg} \ (3)$$

The breakpoint of 52 kg was the local minimum of the TBP formula as a function of weight. The breakpoint of 57.7 was a point of inflection as the TBP curve moves from concave up to concave down. Similar formulas were developed for TBP functions for the normal and high BMI categories and are listed in Table 3.

### Maternal FFM-FM relation

As described in Overview of Model Development and Validation, we sought the function derivation that related FFM to gestational weight so that we could algebraically arrive at a relation between FFM and FM. In the preceding 2 sections, we developed formulas that directly related TBW and TBP to gestational weight. An FFM function of FM could be determined algebraically by a 2-step procedure. The first step was to substitute the formulas developed in the previous 2 sections into the expressions:

$$\Delta \text{TBW} = \text{TBW}_W - \text{TBW}(W_0) \ (4)$$

$$\Delta \text{TBP} = \text{TBP}_W - \text{TBP}(W_0) \ (5)$$

where the zero subscript represents measurements in the prepregnancy state, and the subscript W represents gestational weight at the time of observation. Second, we substituted the expression $W = \text{FFM} + \text{FM}$ into the relation $\text{FFM} = \text{FFM}_0 + \Delta \text{TBW}_W + \Delta \text{TBP}_W$, which yielded the algebraic equations:

$$\text{FFM} = \text{FFM}_0 + \Delta \text{TBW}_W + \Delta \text{TBP}_W \ (6)$$

where $\text{FFM}_0$ is the pregravid state FFM, $\text{FFM}_W$ is the FFM at gestational weight $W$, and $\Delta \text{TBW}_W$ and $\Delta \text{TBP}_W$ are the changes in TBW and TBP from the pregravid state to gestational weight $W$.

**TABLE 3**

| Pregravid BMI classification | TBP by BMI classification expressed as a function of gestational weight
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;19.8 kg/m²)</td>
<td>TBP = -0.04762W + 9.28 if $W \leq 52$, 0.105263W + 1.33 if $52 &lt; W \leq 57.7$, and 0.075472W + 3.05 if $W &gt; 57.7$</td>
</tr>
<tr>
<td>Normal (19.8–26 kg/m²)</td>
<td>TBP = -0.667W + 47.533 if $W \leq 60.2$, 0.0204W + 6.17 if $60.2 &lt; W \leq 65.1$, and 0.0724W + 3.05 if $W &gt; 65.1$</td>
</tr>
<tr>
<td>High (≥26 kg/m²)</td>
<td>TBP = -0.03226W + 10.43871 if $W \leq 81.8$, 0.1W − 0.38 if $81.8 &lt; W \leq 85.8$, and 0.098765W + 0.27407 if $W &gt; 85.8$</td>
</tr>
</tbody>
</table>

$^1$ TBP and $W$ are in kilograms. TBP functions were derived from longitudinal pregnancy data obtained from study data of Butte et al (24, 25). Study data suggested a continuous cubic trend. For mathematical tractability, we approximated the cubic as a piecewise linear function. Break points represent the local minimum, inflection point, and local maximum of the cubic function. TBP, total body protein; $W$, weight.
Maternal TEE function

With application of TEE data (25), we developed 3 pre-pregnancy BMI-dependent functions of TEE dependent on FFM and FM. The TEE function is linearly related to FFM. Because FFM in the previous section is a nonlinear function of FM, TEE is a function of both FFM and FM when fully expanded in the low-, normal-, and high-BMI categories (see supplemental material under “Supplemental data” in the online issue for a description of this expansion). The estimate of prepregnancy TEE captures the variability in energy expenditure in different women at baseline, and this variability was assumed to mirror differences in activity during pregnancy.

Maternal body energy stores (ES)

Similar to nonpregnancy energy-balance models (10, 12), the ES term defined in Equation I was separated into 2 compartments of body energy as FFM and FM. The energy density of FM has been well established and documented in the literature as ~9500 kcal/kg (29). Because of changes in body composition, the energy density of FFM differs throughout pregnancy (22), and therefore, we derived mean trimester-dependent values. Analysis of the longitudinal study data revealed that, on average, 16.7% of FFM during pregnancy consists of protein (24, 25). We assumed that the glycogen content was 0.93% of FFM on the basis of nonpregnant human data (30). We calculated the energy density of FFM by using an energy density of 4380 kcal/kg for protein and 4200 kcal/kg for glycogen (31) to arrive at the average estimated energy density of a kilogram of FFM during pregnancy, ignoring contributions of other minor constituents, as follows:

\[
\text{FFM energy density} = 4380 \times 0.167 + 0.0093 \\
\times 4200 = 771 \text{kcal/kg (9)}
\]

We expanded the ES term into the instantaneous change of the sum of the 2 compartments, FFM and FM, by multiplying by their respective energy densities to arrive at

\[
\text{ES} = [771 \times (d\text{FFM}/dt)] + [9500 \times (d\text{FM}/dt)] (10)
\]

where dFFM/dt and dFM/dt represent the derivatives of FFM and FM, respectively.

Model simulations and statistical analysis

Model simulations were conducted by using the Maple 12 differential equation solver software package (2008; Maplesoft Inc). After input of pregravid age, height, weight, and EI, the differential equation model was numerically simulated by using a fourth-order Runge-Kutta numerical integration in the Maple 12 differential equation solver software package. Inversion of the algebraic equations was obtained by using the algebraic solver package contained in the Maple 12 software.

For Web-based use, a Java programmed applet (2010; Oracle) was developed that used a second-order Newton’s method for solution of algebraic equations and a fourth-order Runge-Kutta’s method for differential equation integration.

RESULTS

Dynamic pregnancy energy-balance model for pregnancy

Three separate differential-equation energy-balance models were developed to predict gestational weight at any time during pregnancy on the basis of the pre-pregnancy BMI categories of low BMI (≤19.8), normal BMI (19.8–26), and high BMI (>26). Solutions to the model provided predictions of maternal FFM and FM at any time during pregnancy. The values for FFM and FM were then applied to predict TEE, TBW, and TBP. Model simulations required inputs of pregravid age, height, and weight. With the variation of trimester-dependent energy intake (in kcal/d), the model predicted the resulting gestational weight as a continuous function of gestational duration (in d). A glossary of all model variables appears in Appendix A.

Model validation

The first step to establish model validity was to observe whether simulated curves generated physiologically plausible results. Most model inputs resulted in sigmoidal GWG curves that agreed with experimentally observed GWG data (28). Moreover, by using different hypothetical combinations of energy intake in each trimester, we were able to generate linear, concave, and convex GWG curves, all of which have been clinically observed (32).

Next, we tested whether the model fit the data used for construction, which we referred to as model calibration. The model was simulated after the input of mean group age, height, pregravid weight, and total energy requirement (equivalent to EI) data reported in the longitudinal pregnancy study (24, 25). The resulting model predictions of weight were compared with actual observed mean weights and yielded close agreement (within 1 kg of gestational weight) at all time points and for all BMI classifications (Figure 1).

Finally, we compared model predictions to the 2 independent pregnancy data sets (22, 23). Group mean pregravid ages, heights, and weights were entered into the model. Because dietary intake was not available for these studies, we applied the same group mean EI by trimester used in the simulations, with assumption of similar average total energy requirements. Model predictions of weight, TBW, FFM, and FM all were within 1 kg of the reported group means (Figure 2).

Model predictions for low-, normal-, and high-BMI categories

We showed the model application by simulating cases for 4 different hypothetical women with different pregravid BMI classifications to arrive at a dietary energy prescription that would achieve the 2009 IOM GWG targets (Table 4). The simulations provided individualized EI ranges to achieve the IOM-recommended GWG range for each subject.

Simulations on the basis of recommended dietary energy intake during pregnancy

Past guidelines for the additional energy intake during pregnancy vary; however, the most widely cited recommendation stated that women should consume an additional 300 kcal/d during pregnancy (28, 32). Model simulations that applied this
constant rule for a normal-weight woman yielded GWGs greater than the 2009 IOM target weights during the first 2 trimesters and fell short at the end of the third trimester (Figure 3A). The current 2002 IOM Dietary Reference Intake for pregnancy stipulates an additional 340 and 452 kcal/d during the second and third trimesters, respectively (34). The application of Dietary Reference Intakes for energy intakes during the second and third trimesters yielded GWG predictions within the current 2009 IOM target GWG range (Figure 3B). Finally, a recent FAO/WHO/United Nations University report (33) recommended that normal-weight women consume an additional 117, 360, and 475 kcal/d during the first, second, and third trimesters, respectively. Model simulations of a normal-weight woman who consumed these additional energy intakes resulted in GWGs within the target IOM ranges (Figure 3C) (3). Thus, model predictions that used current dietary energy intake recommendations coincided with the current IOM target GWG ranges.

**Applet development**

An applet of our dynamic mathematical model for pregnancy can be viewed and used at http://www.pbrc.edu/the-research/tools/GWG-predictor/. The applet requires input of pregravid age, height, weight, and trimester-specific average EI to generate model-predicted GWG curves (Figure 4).
DISCUSSION

To our knowledge, our dynamic mathematical model for pregnancy represents the first validated model that simulates the impact of changes in dietary energy intake on GWG. The model generates physiologically plausible curves that describe weight changes induced by changes in energy intake. The publicly available Web-based delivery system (http://www.pbrc.edu/the-research/tools/GWG-predictor/) provides a useful tool for clinical application.

Given the large number of pregnant women who do not gain within recommended GWG ranges, it behooves the research and clinical community to develop effective interventions that encourage women to gain within guidelines in sometimes challenging environments. Although positive maternal and infant outcomes can be achieved at various GWGs, the recommended weight-gain ranges are those most consistently associated with favorable outcomes. The recent 2009 IOM GWG guidelines (3) called for the provision of individualized care during pregnancy.

TABLE 4
Model simulation of dietary energy-intake ranges predicted to achieve the 2009 IOM GWG target ranges in 4 hypothetical women with different pregravid BMIs

<table>
<thead>
<tr>
<th>BMI classification</th>
<th>Pregravid weight kg</th>
<th>Pregravid BMI kg/m²</th>
<th>Target GWG (kg) by trimester</th>
<th>Model-predicted ΔEI kcal/d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2–3</td>
</tr>
<tr>
<td>Underweight (&lt;18.5 kg/m²)</td>
<td>45</td>
<td>16.9</td>
<td>0.5–2.0</td>
<td>11.4–15.8</td>
</tr>
<tr>
<td>Normal (18.5–24.9 kg/m²)</td>
<td>55</td>
<td>20.7</td>
<td>0.5–2.0</td>
<td>9.1–13.0</td>
</tr>
<tr>
<td>Overweight (25.0–29.9 kg/m²)</td>
<td>72</td>
<td>27.1</td>
<td>0.5–2.0</td>
<td>6.0–8.6</td>
</tr>
<tr>
<td>Obese (&gt;30.0 kg/m²)</td>
<td>97</td>
<td>36.5</td>
<td>0.5–2.0</td>
<td>4.4–7.0</td>
</tr>
</tbody>
</table>

ΔEI, change in energy intake; GWG, gestational weight gain; IOM, Institute of Medicine.

FIGURE 3. Model-predicted GWG compared with gestational duration on the basis of simulations of different energy-intake recommendations for a normal-weight woman [age: 32 y; height: 163 cm; BMI (in kg/m²): 23]. Dashed lines represent lower and upper ranges of the 2009 IOM-recommended GWG (in kg) (3). A: Model prediction of GWG that applied an additional intake of 300 kcal/d (28, 32). B: Model simulations that applied an IOM dietary reference additional energy intake (340 kcal/d in the second trimester and 460 kcal/d in the third trimester); the WHO recommendation (33) of an additional 117-kcal/d energy intake was assumed in the first trimester. C: Model simulations for the FAO/WHO/United Nations University (33) recommended additional energy intake of 117, 360, and 475 kcal/d in the first, second, and third trimesters, respectively. GWG, gestational weight gain; IOM, Institute of Medicine.
for all women to promote GWG within guidelines. Health care providers are encouraged to plot weight gain at each prenatal visit as the basis for discussion of GWG goals and progress toward these goals. There exists a series of free Web-based charts that allow individuals to compare their individual GWG with IOM guidelines. In addition, there exist several calculators that rely on nonpregnancy resting metabolic rate models to estimate required EI to remain within the guidelines. Our applet advances these existing resources by providing the first equation, to our knowledge, developed specifically to model pregnancy related changes to body composition and energy expenditures. Our mathematical model can be used for individualized counseling on the dietary energy intake required to achieve GWG goals and provide continuous objective feedback during pregnancy. Counseling can be accomplished by copying and pasting predicted weights posted in the applet table into a spreadsheet that contains the individual patient weekly weights.

Our mathematical model predicts the impact of changes in dietary energy intake on GWG. Future extensions of our model might include the impact of changes in physical activity on GWG. Our mathematical model was built by using data from healthy, active pregnant adult women with a mean physical activity level (the ratio of TEE to basal metabolic rate) of 1.7 and 1.6 in the second and third trimesters, respectively. These physical activity levels are consistent with average physical activity levels in adult women from industrialized countries (33).

Although the models were developed by using the 1990 IOM BMI classifications, this did not affect the reporting of model predictions by using the revised 2009 IOM classifications (3). The developed applet identifies the user’s BMI classification from the revised 2009 IOM guidelines (3), which classified 4 BMI categories as underweight BMI ($<18.5$), normal BMI (18.5–24.9), overweight BMI (25.0–29.9), and obese BMI ($\geq 30.0$). However, the data set of Butte et al (24, 25) did not contain a sufficient number of subjects classified as obese for model development in this BMI category. With the growing prevalence of obesity within the reproductive female population, it is probably important to develop a distinct model for women classified as obese. As additional maternal body-composition and energy-expenditure data from women classified as obese are acquired, the development of a separate model that considers pregravid BMI $>30$ is an important direction for model improvement.

The need of the particular data required for model validation has been noted previously (3, 35). Finally, although we were only able to validate the model by using 2 studies, the consistency of the results supported the strength of our approach.

In conclusion, our energy-balance model provides plausible predictions of GWG that results from changes in energy intake. Because the model was implemented as a Web-based applet, it can be widely used by pregnant women and their health care providers.

The authors’ responsibilities were as follows—DMT, JEN-B, DER, SBH, LMC, and NFB: conceived the energy-balance model-development strategy for application during pregnancy; DMT, SAL, and NFB: formulated the model and validation studies; CB, LMR, and CKM: contributed to the model
development and initial design of the Web-based delivery system for clinical application; and CB: provided model simulations and developed the Web-based applet. None of the authors had a conflict of interest.

REFERENCES