Evaluation of bioimpedance spectroscopy for measurements of body water distribution in healthy women before, during, and after pregnancy

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Lof, Marie, and Elisabet Forsum. Evaluation of bioimpedance spectroscopy for measurements of body water distribution in healthy women before, during, and after pregnancy. J Appl Physiol 96: 967–973, 2004. First published November 21, 2003; 10.1152/japplphysiol.00900.2003.—Bioimpedance spectroscopy (BIS) is a technique of interest in the study of human pregnancy because it can assess extracellular (ECW), intracellular (ICW), and total body water (TBW) as ECW plus ICW. The technique requires appropriate resistivity coefficients and has not been sufficiently evaluated during the reproductive cycle. Therefore, in a methodological study, we estimated ECW, ICW, and TBW, by means of BIS, and compared the results with the corresponding estimates obtained by using reference methods. Furthermore, results obtained by means of population-specific resistivity coefficients were compared with results obtained by means of general resistivity coefficients. These comparisons were made before pregnancy, in gestational weeks 14 and 32, as well as 2 wk postpartum in 21 healthy women. The reference methods were isotope and bromide dilution. Average ICW, ECW, and TBW, estimated by means of BIS, were in agreement with reference data before pregnancy, in gestational week 14, and postpartum. The corresponding comparison in gestational week 32 showed good agreement for ICW, whereas estimates by means of BIS were significantly (P < 0.001) lower than the corresponding reference values for ECW and TBW. Thus the BIS technique, which was based on a model developed for the nonpregnant body, estimated increases in ICW accurately, whereas increases in ECW and TBW tended to be underestimated. Estimates obtained by using population-specific and general resistivity coefficients were very similar. In conclusion, the results indicated that BIS is potentially useful for studies during pregnancy but that further work is needed before it can be generally applied in such studies.

extracellular water; gestation; intracellular water; total body water

IT IS WELL KNOWN THAT THE NUTRITIONAL situation of the mother is of importance regarding the growth of her fetus. This relationship is important, because size at birth is related to health later in life. Thus a low birth weight has been associated with an increased risk for heart disease, hypertension, and diabetes in adult life (20), whereas a high birth weight may increase the risk for several kinds of cancer in adulthood (1). Furthermore, the nutritional situation throughout the reproductive cycle is important for the health of the mother herself, because being overweight or obese at the start of pregnancy as well as having a large gestational weight gain are associated with increased risks for pregnancy-induced hypertension and gestational diabetes (11). Consequently, studies of the nutritional situation of women during reproduction are important.

Measurements of body composition are fundamental in all studies where the nutritional status of population groups is assessed and especially so during pregnancy when the body fat content changes rapidly. Another interesting variable during pregnancy is the amount of extracellular water (ECW) in the body. This is because human pregnancy may be complicated by preeclampsia or eclampsia, a condition with an incompletely understood etiology. Women suffering from this condition show signs of edema and have a reduced plasma volume expansion compared with healthy pregnant women (17). This is important because poor plasma volume expansion has been associated with poor fetal growth (21). Considering these facts, the so-called bioimpedance spectroscopy (BIS) technique is of interest. This technique, which is based on the conductive properties of body tissues, is able to estimate the amounts of ECW and intracellular water (ICW) in the body and hence the total body water (TBW), calculated as the sum of ECW and ICW (7). The latter is important because estimates of body fat are commonly based on assessments of TBW. Several related techniques based on the conductive properties of the body have been used to study TBW and ECW of pregnant women. For example, Valensise et al. (26) reported that the multifrequency bioimpedance technique can be used to monitor variations in body water compartments in normal pregnancy and to detect abnormal changes in body water distribution in women with gestational hypertension. Furthermore, Ghezzi et al. (10) showed that bioelectrical impedance indexes of pregnant women were significant predictors of birth weight. Although relationships between estimates obtained by means of bioimpedance and body water compartments have not been fully established during pregnancy, these results do indicate that techniques based on the conductive properties of tissues have a potential for use in studies of human pregnancy.

The BIS technique is based on the principles that tissues containing water and electrolytes are more conductive than bone and fat and that the volume of a conductive tissue can be deduced from its resistance (2). By measuring resistance at low and high frequencies, BIS provides estimates of ECW as well as of ICW, because, at low frequencies, the flow of the current through the cell is blocked, whereas at higher frequencies it flows through both the extracellular and intracellular space (7). The technique is noninvasive, very easy to use, may be repeated several times in the same subject, involves no health hazards, and, therefore, represents an ideal method for studies of pregnant women. The convenience of the technique is of special interest, because simple and accurate methods for assessing TBW, ECW, and ICW during pregnancy in the...
clinical situation are presently lacking. However, although several studies have shown that BIS is able to provide accurate results in healthy adults (28, 29), the method has so far been evaluated in only one group of pregnant women. In that study, average values of TBW and ECW obtained by means of BIS in gestational weeks 24–26 and 34–36, as well as 4–6 wk postpartum, were in good agreement with corresponding results obtained by means of reference methods. However, no comparable data for the first one-half of pregnancy have been reported. Furthermore, the potential of BIS to assess ICW during reproduction has not been studied, and no data regarding the ability of BIS to assess changes in ECW and ICW, or in TBW, during pregnancy are available.

In the BIS technique, so-called resistivity coefficients are needed to calculate tissue volumes from resistance, and commonly used coefficients are intended for the average healthy adult. However, resistivity coefficients are influenced by the body composition of the subject under study (6). This point was noted by van Loan et al. (27) when evaluating BIS in pregnant women. Thus these authors calculated resistivity coefficients, specific for their population of women, which they used when evaluating BIS during pregnancy. These population-specific resistivity coefficients made it possible to successfully predict both ECW and TBW before, during, and after pregnancy. The BIS results were apparently calculated by the same model on all occasions. Thus ECW, ICW, and TBW could be calculated in pregnant women by a model developed for nonpregnant subjects, if population-specific resistivity coefficients were used. The study was, however, based on a limited number of women, and the authors emphasized the need for more research in the area (27).

The aims of this study were to evaluate the potential of BIS, by using a model developed for the nonpregnant body, to estimate ECW, ICW, and TBW before conception, during early and late pregnancy, and postpartum, as well as to evaluate its potential to estimate changes in these variables during the reproductive cycle; and to compare results for ECW, ICW, and TBW as obtained by means of BIS, by using resistivity coefficients calculated for our specific population, with the corresponding results obtained when generally applied resistivity coefficients, as provided by the manufacturer of the BIS analyzer, were used.

MATERIALS AND METHODS

Subjects. Twenty-one healthy women planning pregnancy and living in the Linkoping area participated in this study. They were recruited by means of advertisements in the local press and through the health care system. When a woman had conceived, the gestational age was estimated on the basis of an ultrasound measurement, generally in gestational week 12. During pregnancy, no woman was diagnosed with proteinuria, generalized edema, preeclampsia, or eclampsia. All women delivered healthy babies. The study was approved by the ethics committee at the University of Linkoping and informed consent was obtained from all subjects.

Protocol. The women were studied before conception, in gestational weeks 14 and 32, as well as 2 wk postpartum. The following procedure was repeated on each occasion. After an overnight fast, the subject arrived at the hospital by car. After drawing a venous blood sample, the subject was given an oral dose of sodium bromide, and her ECW and ICW were measured by using BIS. An oral dose of stable isotopes was then given to the subject. Another blood sample was obtained 4 h after the dose of sodium bromide, making it possible to estimate the subject’s ECW by means of bromide dilution (ECW_{ref}). During the next 14 days, the subject collected five urine samples to estimate TBW by means of isotope dilution (TBW_{ref}).

Isotope dilution. Each subject was given an accurately weighed dose of $^3$H$_2$O and H$_2^{18}$O (0.05 and 0.15 g/kg body wt, respectively) after collection of two or three background urine samples during a 2- to 7-day period before dosing. Another five urine samples were collected on days 1, 4, 8, 11, and 15 days after the day of dosing. The date and time of day when a sample was collected was always noted. The same procedure was repeated at all measurements, but only $^3$H$_2$O was given at the postpartum measurement. Urine samples were stored in glass vials with internal aluminum-lined screw cap sealing at +4°C until sample collection was completed. They were then stored at −20°C until analyzed. Isotopic enrichments of dose and urine samples were analyzed by an isotopic ratio mass spectrometer fitted with a CO$_2$/H$_2$/H$_2$O equilibrium device (Deltaplus XL, Thermoquest, Bremen, Germany). The procedure described by Thielecke and Noack (25) was followed, except that equilibration time was 180 and 840 min for H$_2$O and CO$_2$, respectively. Isotope dilution dilutions (N$_D$/N$_O$) were calculated from zero-time enrichments obtained from the exponential isotope disappearance curves that provided estimates for the rate constants, $k_D$ and $k_O$, for $^3$H and $^{18}$O, respectively. The mass spectrometric response was standardized using Vienna standard marine air (VSMA) for dose and urine samples from the same subject were always analyzed on the same occasion within the same equilibrium device when a linear mass spectrometric response was also confirmed for both isotopes. Analytic precision in the measurement range, for results expressed as mole fraction, was 0.44 ppm for $^3$H and 0.15 ppm for $^{18}$O. N$_D$/N$_O$ for our 21 subjects was 1.037 ± 0.007, 1.029 ± 0.008, and 1.027 ± 0.008 before pregnancy and in gestational weeks 14 and 32, respectively. Before pregnancy and in gestational weeks 14 and 32, TBW_{ref} was the average of N$_D$/N$_O$1.04 and N$_D$/N$_O$1.01, whereas it was N$_D$/N$_O$1.04 postpartum.

Bromide dilution. Each subject was given an accurately weighed dose of sodium bromide (40 mg sodium bromide/kg body wt). Bromide concentration in dose and serum samples was analyzed by using a spectrophotometric procedure based on the formation of a gold bromide complex (24). Bromide space was calculated as dose of bromide/the concentration of bromide in serum at 4 h postdose — the concentration of bromide in the baseline serum sample). ECW_{ref} was calculated as bromide space $\times 0.90 \times 0.95 \times 0.94$ (3).

BIS. The measurements were performed with careful attention to the instructions provided by the manufacturer of the equipment used (Hydra EC/ICF model 4200 with Hydra BIS 4200 Software Utilities, Xitron Technologies, San Diego, CA). Thus, after body weight was recorded, the subject was placed in a supine position with her arms abducted from her body and her legs separated. Two electrodes were placed 5 cm apart on the dorsal surface of the right hand and another two on the right foot. The software estimated the resistance of ECW and of ICW on the basis of measurements of resistance and reactance at 50 frequencies between 5 kHz and 1 MHz with the Cole model (5). The accuracy of the fit to the Cole model was rated as excellent for all measurements by the software. ECW and ICW were calculated, by means of the software, from their resistances using equations based on the Hanai mixture theory (12). For these calculations, general resistivity coefficients, as provided by the manufacturer (39.00 and 264.90 $\Omega$·cm for ECW and ICW, respectively), as well as resistivity coefficients calculated especially for the women in our study, were used. The latter were calculated by using the software described above, using TBW_{ref}, ECW_{ref}, and the resistance of ECW and ICW, respectively, as measured by means of the Hydra equipment, for our 21 subjects before conception. These population-specific resistivity coefficients were 39.61 $\Omega$·cm for ECW and 269.57 $\Omega$·cm for ICW. ECW, ICW, and TBW calculated using the resistivity coefficients provided by Xitron Technologies will be referred to as TBW_{XT}, ECW_{XT}, and ICW_{XT}, respectively, whereas the corresponding figures obtained using the
Significance correlation analyses were performed as described by Hassard (13). Ined according to Bland and Altman (4). Linear regression and subsequent post hoc analysis using Tukey between group averages were identified (StatSoft, Scandinavia, Uppsala, Sweden).

Body weight, kg 67.6

Population-specific resistivity coefficients are labeled TBW_{PS}, ECW_{PS}, and ICW_{PS}, respectively.

Body weight and height. The body weight of the women in light underwear was recorded at the different measurements on a high-precision scale (KCC 150, Mettler-Toledo). Their body weights were also recorded in the delivery room before childbirth. Height was measured by a wall stadiometer.

Statistics. Values given are means ± SD. Significant differences between group averages were identified by repeated ANOVA and subsequent post hoc analysis using Tukey’s multiple-comparison test (13). Paired t-test (13) was also used. Agreement between results obtained with BIS and the appropriate reference methods was examined according to Bland and Altman (4). Linear regression and correlation analyses were performed as described by Hassard (13). Significance was accepted at the P < 0.05 level. All statistical analyses were carried out by using Statistica software, 6.0 version (StatSoft, Scandinavia, Uppsala, Sweden).

RESULTS

Characteristics of subjects. The characteristics of the women before conception, as well as their weight gain during the complete pregnancy, length of gestation, and birth weight of their babies are presented in Table 1. The women varied considerably with respect to body weight and body mass index before conception, and they gained 17.5 ± 6.7 kg during the complete pregnancy. Compared with the figures before conception, their body weight had increased by 2.3 ± 2.5, 11.5 ± 5.0, and 6.1 ± 5.7 kg in gestational weeks 14 and 32 and 2 wk postpartum, respectively. ECW_{ref} as a fraction of TBW_{ref} increased from 43.8 ± 3.2% before conception to 45.6 ± 4.2, 48.2 ± 4.3, and 45.6 ± 3.7% in gestational weeks 14 and 32 and 2 wk postpartum, respectively. This increase was significant (P < 0.05) in gestational week 32. The resistances of ECW and ICW as obtained for the subjects by means of BIS at the different measurements are given in Table 2.

EC.W. Table 2 shows ECW_{XT}, ECW_{PS}, and ECW_{ref} before, during, and after pregnancy. ECW_{XT} was significantly lower than ECW_{ref} in gestational weeks 14 and 32, as well as 2 wk postpartum, whereas ECW_{PS} was significantly lower than ECW_{ref} in gestational week 32 and 2 wk postpartum. Average ECW_{PS} was similar to average ECW_{XT} at all four measurements. ECW_{XT} is compared with ECW_{ref} according to Bland and Altman, at the different stages of reproduction in Table 3 and in Fig. 1. The mean differences between ECW_{XT} and ECW_{ref} were small before conception and in gestational week 14 (−0.13 and −0.84 kg, respectively). However, in gestational week 32, the mean difference was as high as −3.12 kg for ECW_{XT} vs. ECW_{ref}. Moreover, in gestational week 32, ECW_{XT} was lower than ECW_{ref} for all subjects, as shown in Fig. 1. In addition, a significant linear relationship between the average of ECW_{XT} and ECW_{ref} (y) and ECW_{XT} − ECW_{ref} (y) was found (y = −0.342x + 2.800; r = −0.570; P < 0.05). At the measurement 2 wk postpartum, the mean difference was small, and ECW_{XT} − ECW_{ref} was only −0.84 kg (Table 3). As also presented in Table 3, limits of agreement (±2 SD) for ECW_{XT} − ECW_{ref} ranged from ±2.08 to ±3.46 kg at the four different measurements. Results obtained for ECW_{PS} (data not shown) were very similar to those described above for ECW_{XT}. Table 2 also shows that average values for ECW_{ref}, ECW_{XT}, and ECW_{PS} were all higher in gestational weeks 14 and 32, as well as postpartum, compared with the corresponding values obtained before pregnancy. However, Table 4 shows that increases obtained by means of BIS, i.e., using ECW_{XT}, were lower than the corresponding increases obtained by means of the reference method, i.e., using ECW_{ref} in gestational weeks

Table 1. Characteristics of the subjects in the study

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>30</td>
<td>4</td>
<td>23–37</td>
</tr>
<tr>
<td>Body weight before pregnancy, kg</td>
<td>67.6</td>
<td>12.0</td>
<td>51.0–95.0</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.67</td>
<td>0.07</td>
<td>1.54–1.76</td>
</tr>
<tr>
<td>Body mass index before pregnancy, kg/m²</td>
<td>24.3</td>
<td>5.0</td>
<td>17.6–39.0</td>
</tr>
<tr>
<td>Weight gain during the complete pregnancy, kg</td>
<td>17.5</td>
<td>6.7</td>
<td>7.9–29.1</td>
</tr>
<tr>
<td>Birth weight of baby, g</td>
<td>3.720</td>
<td>500</td>
<td>2,600–4,540</td>
</tr>
<tr>
<td>Length of gestation, days</td>
<td>279</td>
<td>9</td>
<td>256–5296</td>
</tr>
</tbody>
</table>

n = 21 subjects.

Table 2. Resistance of ECW and ICW, body weight, ECW, ICW, and TBW before pregnancy, in gestational weeks 14 and 32, as well as 2 wk postpartum, in the women in the study

<table>
<thead>
<tr>
<th></th>
<th>Before Conception</th>
<th>Gestational Week 14</th>
<th>Gestational Week 32</th>
<th>2 wk Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>R_{ECW}, Ω</td>
<td>740.8 ± 90.7</td>
<td>726.9 ± 83.1</td>
<td>661.1 ± 75.8</td>
<td>700.9 ± 83.2</td>
</tr>
<tr>
<td>R_{ICW}, Ω</td>
<td>1,558.2 ± 232.8</td>
<td>1,578.2 ± 216.8</td>
<td>1,436.5 ± 224.6</td>
<td>1,480.5 ± 233.8</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>67.6 ± 12.0</td>
<td>69.9 ± 12.9</td>
<td>79.2 ± 13.2</td>
<td>73.8 ± 13.5</td>
</tr>
<tr>
<td>ECW_{ref}, kg</td>
<td>14.0 ± 1.94</td>
<td>15.0 ± 2.30</td>
<td>18.8 ± 2.91</td>
<td>15.6 ± 1.95</td>
</tr>
<tr>
<td>ECW_{XT}, kg</td>
<td>13.87 ± 2.03</td>
<td>14.18 ± 2.04</td>
<td>15.72 ± 2.10</td>
<td>14.82 ± 2.10</td>
</tr>
<tr>
<td>ECW_{PS}, kg</td>
<td>14.01 ± 2.04</td>
<td>14.32 ± 2.06</td>
<td>15.89 ± 2.11</td>
<td>14.95 ± 2.15</td>
</tr>
<tr>
<td>ICW_{ref}, kg</td>
<td>17.96 ± 2.38</td>
<td>17.93 ± 2.88</td>
<td>20.19 ± 2.45</td>
<td>18.79 ± 3.31</td>
</tr>
<tr>
<td>ICW_{XT}, kg</td>
<td>17.77 ± 2.89</td>
<td>17.63 ± 2.77</td>
<td>19.64 ± 3.28</td>
<td>18.92 ± 3.47</td>
</tr>
<tr>
<td>ICW_{PS}, kg</td>
<td>17.96 ± 2.92</td>
<td>17.83 ± 2.81</td>
<td>19.88 ± 3.31</td>
<td>19.12 ± 3.36</td>
</tr>
<tr>
<td>TBW_{ref}, kg</td>
<td>31.97 ± 3.82</td>
<td>32.94 ± 4.23</td>
<td>39.04 ± 4.16</td>
<td>34.44 ± 4.67</td>
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<tr>
<td>TBW_{XT}, kg</td>
<td>31.64 ± 4.75</td>
<td>31.81 ± 4.61</td>
<td>35.29 ± 5.24</td>
<td>33.74 ± 5.38</td>
</tr>
<tr>
<td>TBW_{PS}, kg</td>
<td>31.97 ± 4.80</td>
<td>32.15 ± 4.67</td>
<td>35.77 ± 5.25</td>
<td>34.07 ± 5.32</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 21 subjects. R_{ECW}, resistance of extracellular water (ECW); R_{ICW}, resistance of intracellular water (ICW); TBW, total body water; ECW_{ref}, ICW_{ref}, TBW_{ref}; ECW, ICW, and TBW values, respectively, obtained by means of reference methods, i.e., bromide dilution, isotope dilution, or a combination of these; ECW_{XT}, ICW_{XT}, TBW_{XT}; ECW, ICW, and TBW calculations, respectively, were performed by using general resistivity coefficients as provided by Xitron Technologies; ECW_{PS}, ICW_{PS}, TBW_{PS}; ECW, ICW, and TBW calculations, respectively, were performed by using population-specific resistivity coefficients. *Significantly different from corresponding value obtained before pregnancy, P < 0.001. **Significantly different from corresponding value obtained before pregnancy, P < 0.05. $Significantly different from the corresponding value for ECW_{ref}, P < 0.05. "Significantly different from the corresponding value for ECW_{ref}, P < 0.01. †Significantly different from the corresponding value for TBW_{ref}, P < 0.05. ‡Significantly different from the corresponding value for TBW_{ref}, P < 0.001.

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Table 3. Comparison of ECW obtained by using BIS vs. reference data according to Bland and Altman (4) at different stages of reproduction in the women in the study. *P < 0.05.

Table 4. Increases vs. the prepregnant value in ECW, ICW, and TBW, as estimated by using BIS and reference methods in gestational weeks 14 and 32, as well as 2 wk postpartum in the subjects in the study.

Table 5. Comparison of TBW obtained using BIS vs. reference data, according to Bland and Altman (4), at different stages of reproduction in the women in the study.
for \( \text{TBW}_{\text{XT}} - \text{TBW}_{\text{ref}} \) ranged from \( \pm 4.66 \) to \( \pm 5.88 \) kg at the four different measurements (Table 5). No significant linear relationships between the average of \( \text{TBW}_{\text{XT}} \) and \( \text{TBW}_{\text{ref}} \) (\( x \)) and \( \text{TBW}_{\text{XT}} - \text{TBW}_{\text{ref}} \) (\( y \)) were found at any of the measurements. Results obtained for \( \text{TBW}_{\text{PS}} \) (data not shown) were very similar to those described above for \( \text{TBW}_{\text{XT}} \). Table 2 also shows that average values for \( \text{TBW}_{\text{ref}}, \text{TBW}_{\text{XT}}, \) and \( \text{TBW}_{\text{PS}} \) were all higher in gestational weeks 14 and 32, as well as 2 wk postpartum compared with the corresponding values obtained before pregnancy. However, as shown in Table 4, such increases obtained by means of BIS, i.e., using \( \text{TBW}_{\text{XT}} \), were lower than the corresponding increases obtained by means of the reference method, i.e., using \( \text{TBW}_{\text{ref}} \) in gestational weeks 14 and 32, as well as 2 wk postpartum, and these two ways of measuring increases in TBW produced significantly different results in gestational week 32. The corresponding results for \( \text{TBW}_{\text{PS}} \) (data not shown) were very similar to those shown in Table 4 for \( \text{TBW}_{\text{XT}} \).

**DISCUSSION**

The average weight gain during pregnancy for our subjects is higher than the weight gain recommended by the Institute of Medicine (15). However, although no comprehensive data on gestational weight gain by Swedish women have been reported recently, smaller studies suggest that Swedish women, compared with other Western women, tend to gain slightly more weight during pregnancy (19, 23). Nevertheless, the gestational weight gain observed in this study must be considered as higher than that for Swedish women in general. Our women gained \( \sim 7 \) kg of TBW during the first 32 wk of pregnancy, which is somewhat higher than the corresponding estimate made by Hytten (14). Furthermore, our subjects had gained almost 5 kg of ECW in gestational week 32, which is slightly higher than the corresponding estimate made by Hytten, but in agreement with data from the only longitudinal study where ECW has been measured before and during pregnancy in the same women by using bromide dilution (27).

In the present study, average \( \text{ECW}_{\text{XT}} \) and \( \text{ECW}_{\text{PS}} \), as well as average \( \text{TBW}_{\text{XT}} \) and \( \text{TBW}_{\text{PS}} \), agreed well with corresponding results obtained by means of the reference methods when our subjects were measured before pregnancy. The Bland and Altman comparison showed, however, that the limits of agreement for TBW and ECW (Tables 3 and 5, respectively) were somewhat wider than those reported by van Marken Lichtenbelt et al. (29) in a group of healthy young women. This is probably due to the fact that our subjects were more variable with respect to body weight and body mass index than the subjects studied by van Marken Lichtenbelt et al., since a recent report has indicated that the degree of body fatness affects the accuracy of BIS (6).

The underestimation of TBW and ECW in late pregnancy when BIS was used, as found in the present study, is in contrast to the results of van Loan et al. (27) in American women. It is, therefore, of interest to consider the reference methods used in the two studies. The bromide method as well as the isotope dilution method that were used in both studies represent well-established methods for estimating ECW and TBW (22). However, some minor methodological differences should be pointed out. First, in contrast to van Loan et al. (27), we multiplied bromide space by 0.94 to correct for the water content of serum. However, even without this correction, our BIS measurements underestimated TBW and ECW by \( \sim 3 \) kg in week 32 of pregnancy. Second, we used both \(^2\text{H}\) and \(^18\text{O}\) to estimate \( \text{TBW}_{\text{ref}} \), whereas van Loan et al. used only \(^2\text{H}\). Recalculation of our data using only the \(^2\text{H}\) results changed TBW by \(< 0.4\% \) and did not affect the conclusions presented in this paper. Third, we calculated \( \text{TBW}_{\text{ref}} \) using the back-extrapolation approach, whereas van Loan et al. used both the back-extrapolation and the plateau methods to calculate TBW, although it is not quite clear at which stages of reproduction the respective methods were used. When we recalculated our data using 4-h postdose isotope enrichment results to obtain data comparable to the plateau method, we obtained \( \sim 2\% \) higher TBW. Use of these higher values for TBW did not affect the results and conclusions of this study in any important way. Thus we are unable to show that methodological differences explain the different results obtained in our study compared with the study by van Loan et al. The populations in the two studies were also different. Thus our subjects varied more with respect to body fat content before pregnancy and also had higher gestational weight gains. However, exclusion of the subjects with the highest body fat content (\( > 39\% \)) or subjects with the lowest fat content (\( < 18\% \)) did not change our results. Furthermore, when the eight subjects with the highest gestational weight gains (\( > 23 \) kg) were excluded, BIS still underestimated ECW and TBW to the same extent as reported in Tables 2 and 5. Finally, it is conceivable that the difference in results, as observed in the two studies, is related to the resistivity coefficients used. In our study, the population-specific resistivity coefficients were similar to the general resistivity coefficients provided by the manufacturer of the equipment used. Consequently, \( \text{ECW}_{\text{PS}} \) was similar to \( \text{ECW}_{\text{XT}} \), \( \text{ICW}_{\text{PS}} \) was similar to \( \text{ICW}_{\text{XT}} \), and hence \( \text{TBW}_{\text{PS}} \) was similar to \( \text{TBW}_{\text{XT}} \). These findings are in contrast to those of van Loan et al. (27), in which the use of population-specific resistivity coefficients was essential for the good agreement between BIS and the reference methods before and during pregnancy. Unfortunately, van Loan et al. did not present any values either for their population-specific resistivity coefficients or for the resistivity coefficients provided by the manufacturer of the equipment used.

This study provides some interesting aspects concerning the possibility of assessing ICW during the reproductive cycle. Although we found that the limits of agreement were large for the differences between ICW obtained by means of BIS and the reference methods before, during, and after pregnancy, we also found that average estimates of ICW, obtained by means of BIS, were in good agreement with the corresponding reference data. The large limits of agreement are probably related, at least to some extent, to the relatively large random error in the reference estimates when ICW is assessed as the difference between \( \text{TBW}_{\text{ref}} \) and \( \text{ECW}_{\text{ref}} \) (22). This imprecision in the reference estimates of ICW limits the possibility of assessing the potential of BIS for studying ICW during human reproduction, especially when evaluating its potential for measuring ICW in individual women. However, our data certainly support the conclusion that BIS, based on a model developed for nonpregnant subjects, may be useful for estimating average ICW, as well as changes in ICW, in groups of women during reproduction. In this context, it is relevant to note that Earthman et al. (8) provided evidence showing that BIS could...
accurately assess changes in body cell mass in patients with human immunodeficiency virus infection. Increases in ICW during pregnancy are likely to include changes in the maternal body, for example, increases in mammary and uterine tissues, as well as growth of the fetus and placenta, whereas increases due to maternal blood volume expansion and accumulation of amniotic fluid, for example, would not be included in such estimates. Obtaining valid estimates of ICW may, therefore, represent a new possibility to explore the physiology of human pregnancy in relation to health and disease.

Our results clearly show that BIS, as applied in the present study, is unable to produce valid estimates of ECW in women in gestational week 32. It is, therefore, relevant to consider the model used to calculate body water compartments in this study. This model was developed for the nonpregnant body, which differs in a number of respects from the pregnant body. For example, the model (30) includes a factor allowing for the proportions of the body that may obviously be altered during pregnancy. It is also relevant to note that, as shown in a study on women in gestational weeks 18 and 36 (9), electrolyte concentrations in ECW and ICW change during pregnancy. Nevertheless, in the present study, fairly accurate estimates of ECW and ICW in gestational week 14 and ICW in gestational week 32 were obtained by using the model developed for nonpregnant subjects. This seems to indicate that modifying this model in a way that makes it theoretically valid for pregnant women may not be particularly complicated. In this context, it should also be emphasized that our results showing that the applied model (30) can accurately assess ECW and ICW in gestational week 14 as well as ICW in gestational week 32 are based on empirical evidence only. Until a new model is available that takes the physiological and anatomic situation of pregnant women properly into account, estimates of ECW and ICW during gestation obtained by means of BIS should be interpreted with caution.

It is also important to point out that the model we used to assess body water compartments by means of BIS is based on wrist-ankle measurements of resistance and assumes that the trunk. This suggestion is supported by reports that have pointed out limitations of a technique based on principles similar to those of BIS, i.e., multiple bioimpedance analysis, in which the trunk is connected in a series, in which conductors with the smallest cross-sectional area (i.e., arms and legs) will determine most of the resistance, whereas the part with the largest cross-sectional area (i.e., the trunk) will contribute less (2). This model may not be the most appropriate during pregnancy when a substantial amount of the water retained is located in the trunk. This suggestion is supported by reports that have pointed out limitations of a technique based on principles similar to those of BIS, i.e., multiple bioimpedance analysis, in which the wrist-ankle approach has been used to estimate ECW in patients with ascites (16) and in patients receiving peritoneal dialysis (31). Moreover, Zhu et al. were able to measure changes in ECW in patients during peritoneal dialysis by combining whole body measurements with segmental measurements of the trunk (31). Whether this approach is able to improve the accuracy of BIS in late pregnancy could be the topic for future studies.

In conclusion, when based on a model developed for nonpregnant subjects, the BIS technique produced fairly accurate but imprecise estimates of ECW, ICW, and TBW before pregnancy, in early pregnancy, and postpartum. In late pregnancy, BIS underestimated ECW and TBW while ICW remained accurate. Furthermore, BIS underestimated pregnancy-related increases in ECW and TBW but was able to estimate changes in ICW accurately, which may represent a new possibility for studying the physiology of human pregnancy. All of these findings were the same whether general resistivity coefficients, as provided by the manufacturer of the BIS analyzer, or population-specific resistivity coefficients were used. However, general application of BIS for assessing body water compartments during gestation requires the development of a new model that takes into account the physiological and anatomic changes occurring during pregnancy.

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