Protein metabolism in pregnancy¹–⁴

Satish C Kalhan

ABSTRACT Adaptation to pregnancy involves major changes in maternal metabolism to provide for the growing demands of the conceptus. Although changes in glucose metabolism, and possibly in fatty acid metabolism, occur in parallel with the increasing energy demands of the mother and the fetus, adaptation of protein metabolism appears to be in anticipation of maternal and fetal needs. During pregnancy, there is an excess of maternal nitrogen in the form of lean body mass over that deposited in the fetus and the products of conception; there is also a pregnancy-induced hypoaminoacidemia and a diminished amino acid response to protein intake, suggesting an increased uptake of amino acids in the splanchnic compartment. With the use of stable-isotope-labeled tracers, it was shown that there is a decreased rate of urea synthesis during pregnancy that is evident early in gestation. Kinetic studies of leucine metabolism showed no significant change in leucine carbon turnover but a significantly lower rate of leucine nitrogen turnover, suggesting a lower rate of leucine transamination. These data suggest an integral regulation of whole-body protein and nitrogen metabolism starting early in gestation and aimed at conservation and accretion of nitrogen by the mother and the fetus. Am J Clin Nutr 2000;71(suppl):1249S–55S.

KEY WORDS Pregnancy, protein, urea, stable isotopes, leucine

INTRODUCTION Adaptation to pregnancy in humans involves major anatomic, physiologic, and metabolic changes in the mother to support and provide for her nutritional and metabolic needs and those of the growing conceptus. In this context, data from several studies in humans and in animal models showed that glucose is the primary source of energy for the fetus, whereas accretion of nitrogen and protein is an essential component of fetal growth and synthesis of new fetal and maternal tissues.

With advancing gestation and increasing maternal (plus fetal) weight and as the total rate of energy consumption by the mother (plus fetus) and the greater demands for nutrients by the fetus increase, there is a commensurate increase in total glucose production by the mother, as shown by tracer-isotope-dilution studies (1–5). A similar parallel increase in the flux of alternative fuels—fatty acids (lipolysis)—was shown in human gestation (S Majahan, L Gruca, SC Kalhan, unpublished observations, 1998). Thus, adaptation in the key energy-yielding substrates parallels the increasing demands of pregnancy. This is in contrast with changes in nitrogen and protein metabolism, which appear early in pregnancy, even before there is any significant increase in the mass of the conceptus. Thus, changes in maternal protein and nitrogen metabolism that appear early in gestation may be aimed primarily toward nitrogen accretion by the mother. Studies by Catalano et al (6) showed that, in addition to the increase in pregnancy-related hormones, there is a significant increase in first- and second-phase insulin response to intravenous glucose challenge with advancing gestation in healthy pregnant women. This is accompanied by a decrease in insulin sensitivity as quantified by a decrease in glucose uptake during a hyperinsulinemic euglycemic clamp (6, 7). Although the effect of decreased insulin sensitivity on glucose metabolism can be inferred from the reported physiologic data, the effect on protein metabolism has not been examined. In this context, it is relevant to note that other states of nitrogen accretion and growth (eg, during puberty, in neonates, and during growth hormone replacement therapy) are characterized by resistance to insulin action, specifically in relation to peripheral glucose uptake (8–11).

PROTEIN ACCRETION BY THE MOTHER DURING PREGNANCY Total protein and nitrogen accretion by the mother during pregnancy has been estimated by using several methods, which often have resulted in somewhat conflicting data. As estimated by Pitkin (12), ≈40% of the total weight gain by the mother is represented by the fetus, placenta, and amniotic fluid. The remaining 60% represents maternal tissues, including uterine tissue, breast tissue, blood, adipose tissue, and extracellular fluids. However, these estimates did not include changes in other organs, such as the liver, kidney, and heart, which are also known to increase in size during pregnancy.

Several studies were performed to quantify the composition of weight gain by the mother during pregnancy. These included

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TABLE 1

<table>
<thead>
<tr>
<th>Increases in total body potassium in pregnancy</th>
<th>mmol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placenta</td>
<td>25</td>
</tr>
<tr>
<td>Fetus</td>
<td>150</td>
</tr>
<tr>
<td>Uterus</td>
<td>65</td>
</tr>
<tr>
<td>Red blood cells</td>
<td>25</td>
</tr>
<tr>
<td>Plasma</td>
<td>6</td>
</tr>
<tr>
<td>Others</td>
<td>229</td>
</tr>
<tr>
<td>Total</td>
<td>500</td>
</tr>
</tbody>
</table>

1Data from reference 19.
2Includes cardiac tissue, kidney, and muscle tissue.

nitrogen balance studies and measurements of body compartments (eg, extra- and intracellular water, total body water, and density). In all of these measurements, the fetal compartment is included in the total estimate because most of the tracers used (labeled water, bromide, and total body ⁴₀𝐾 counting) diffuse rapidly across the placenta.

On the basis of data from the nitrogen balance studies, King (13) inferred that nitrogen retention by the mother was in excess of the estimated protein cost of pregnancy. However, the nitrogen balance studies are fraught with inaccuracies, often because of lack of inclusion of nitrogen lost from skin, expired air (ammonia), and other secretions.

Estimates of total body water by use of the stable-isotope tracers ²₂H₂O and H₁₈O can be used to quantify lean body mass, assuming that fatty tissue contains no or very little water (14–18). Critical to this method is the assumption that the water content or the hydration constant of the lean body mass remains unchanged in pregnancy. Because new tissue growth during pregnancy is heterogeneous with varying water content (eg, tissue of the conceptus may have a very high water content compared with that of maternal tissues), these methods of estimation require the use of different hydration constants during pregnancy (15, 17). Nevertheless, these data show that, although there is an increase in total body water with advancing gestation, the fraction of body weight represented by water is the same in pregnant and nonpregnant women (14–16, 18).

Thus, allowing for a small change in the hydration constant (17), the overall proportional increase in fat mass and lean body mass is similar in pregnant and nonpregnant women. These data are strengthened by the energy cost of weight gain (26 kJ/kg) and the energy cost of quiet sitting in pregnant women (100 kJ · min⁻¹ · kg⁻¹ · fat-free wt), values comparable with those of nonpregnant women (19).

Estimates of total body potassium either by isotopic dilution or by ⁴₀𝐾 counting can be used to estimate lean body mass because there is a consistent ratio of potassium to lean body mass (K:LBM) in humans. However, note that K:LBM or K:N of the fetal and maternal tissue deposited during pregnancy was found to be lower than that in healthy adults. Computations made by Forbes (19) on the basis of 4 studies of ⁴₀𝐾 counting during pregnancy are shown in Table 1. The average of these 4 values showed a gain of 500 mmol K during pregnancy. In addition to increases in the placenta, fetus, uterus, red blood cells, and plasma, 229 mmol K was gained by the mother in other tissues. This represents an additional accretion of nitrogen of ~90 g or ~550 g protein equivalents.

PLASMA AMINO ACIDS IN PREGNANCY

Several studies showed that pregnancy is associated with gestation-induced hypoaominoacidemia during fasting, which is evident early in gestation and persists throughout pregnancy (20–23) and has been related to pregnancy-related hormones. In addition, during fasting there is a more profound reduction in glucogenic amino acids—alanine, serine, threonine, glutamine, and glutamate—that has been suggested as being responsible for fasting hypoglycemia during pregnancy (20, 24), although there is no direct evidence to support this. A diminished plasma amino acid response to nutrient uptake suggests an increased splanchnic uptake of amino acids (21). The amounts of circulating amino acids have been related to fetal outcome, particularly to infant birth weight. Specifically, Kalkhoff et al (25) observed a positive correlation between total amino acid concentrations and concentrations of serine, lysine, proline, ornithine, arginine, and neonatal birth weight. These correlations do not necessarily suggest a key role of these amino acids in fetal growth because some of them (eg, serine) are not transported to the fetus in any significant quantities (26). Thus, the changes in the concentration of a particular amino acid may reflect other metabolic processes that may modify the metabolism of that particular amino acid.

NITROGEN METABOLISM IN PREGNANCY

Changes in nitrogen metabolism in human pregnancy have been quantified by using either the traditional nitrogen balance method or, more recently, by using stable-isotope-labeled amino acids and urea to measure whole-body protein and amino acid turnover and oxidation. Because of the problems and errors associated with nitrogen balance studies, recent data, for the most part, were obtained from the isotope-tracer studies. In the following section, only the recent data from the human studies are presented. A more comprehensive review was published previously (27).

UREA SYNTHESIS DURING PREGNANCY

Quantitative estimates of the rates of urea synthesis and excretion have been performed to assess the irreversible nitrogen loss or protein catabolism and oxidation. Previous studies in humans and in rats, either during fasting or in response to exogenously administered amino acids, showed an attenuated rate of urea synthesis during pregnancy (28–30). In addition, in isolated liver preparations from pregnant rats, Metzger et al (29) showed a decreased rate of urea synthesis in response to a supramaximal dose of alanine, even though the rate of glucose production was appropriately increased, suggesting an intrahepatic diversion of nitrogen away from urea synthesis.

In human pregnancy, a lower concentration of blood urea nitrogen is apparent early in gestation and has been attributed to an increase in renal clearance. Kalhan et al (23), using the [¹⁵Ν₂]urea tracer-dilution method, observed an ~30% decrease in the rate of urea synthesis after an overnight fast in healthy and diabetic women during the third trimester of pregnancy. Because pregnancy was associated with a decreased concentration of total α-amino nitrogen in blood, these authors attributed the lower rate of urea synthesis to decreased delivery of ureogenic substrates to the liver. Additionally, >90% of urea synthesized was excreted in the urine, suggesting no significant contribution of enterohepatic recycling (salvage) of urea nitrogen. A similar
PROTEIN METABOLISM IN PREGNANCY

Together, these studies point to a significant adaptive change in urea nitrogen kinetics during pregnancy. Because the major source of urea nitrogen during fasting is the peripherally released amino acids, these data point to adaptive changes in peripheral (muscle) nitrogen kinetics during pregnancy.

**PROTEIN TURNOVER**

Several tracer methods have been used to quantify the dynamic aspects of whole-body protein turnover. These were reviewed extensively and their limitations were discussed (33). With most of these methods, whole-body protein is considered to be a single, well-mixed dynamic pool that is in a constant state of flux or turnover involving breakdown and resynthesis. Thus, a stochastic model (Figure 2) can be used to quantify the rate of protein turnover. Intracellular breakdown of protein will result in the release of free amino acids, which are the precursors for the synthesis of protein. The intracellular amino acid pool is in equilibrium with the extracellular (plasma) amino acids, regulated by the membrane transport characteristics of individual amino acids. Other contributors to the extracellular amino acid pool are the amino acids derived from dietary protein. The amino acids (protein) are catabolized or oxidized and their catabolic and oxidation products are eliminated from the body either as nitrogen (eg, urea or ammonia) or as carbon dioxide in the expired air. During pregnancy, protein turnover in the fetal compartment also contributes to the amino acid flux in the fetus and the mother.

TABLE 2

<table>
<thead>
<tr>
<th></th>
<th>Nonpregnant (n = 8)</th>
<th>Trimester 1 (n = 9)</th>
<th>Trimester 2 (n = 9)</th>
<th>Trimester 3 (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen intake (mg N·kg⁻¹·d⁻¹)</td>
<td>167 ± 36</td>
<td>224 ± 60</td>
<td>266 ± 59</td>
<td>217 ± 49</td>
</tr>
<tr>
<td>Urea production (mg N·kg⁻¹·d⁻¹)</td>
<td>150 ± 38</td>
<td>175 ± 37</td>
<td>168 ± 33</td>
<td>140 ± 23</td>
</tr>
<tr>
<td>Urea excretion (mg N·kg⁻¹·d⁻¹)</td>
<td>110 ± 26</td>
<td>98 ± 35</td>
<td>107 ± 20</td>
<td>89 ± 18</td>
</tr>
<tr>
<td>Production/intake (%)</td>
<td>91 ± 19</td>
<td>81 ± 18</td>
<td>64 ± 13</td>
<td>66 ± 13</td>
</tr>
<tr>
<td>Excretion/intake (%)</td>
<td>66 ± 11</td>
<td>44 ± 14</td>
<td>42 ± 11</td>
<td>42 ± 9</td>
</tr>
</tbody>
</table>

1 ± 5 ± SD. Data from reference 32.
2 Significantly different from nonpregnant women, P < 0.05 (repeated-measures ANOVA).
3 Significantly different from trimester 3, P < 0.05 (repeated-measures ANOVA).

Decrease in urea nitrogen excretion was reported by Denne et al (31) in a later study of healthy pregnant women during the third trimester of pregnancy.

The changes in urea kinetics and salvage during pregnancy were examined by Forrester et al (32) in healthy Jamaican women. Urea nitrogen salvage refers to the rescue of nitrogen released from urea after bacterial hydrolysis in the gastrointestinal tract. It was suggested that the nitrogen derived from salvaged urea might contribute to the nitrogen economy of the body and may be an important feature of adaptive process to conserve nitrogen, particularly during low protein intake (32). Forrester et al measured urea kinetics over a 24-h period while the subjects were consuming a diet consisting of previously determined habitual protein and energy intakes. Rates of urea synthesis, excretion, and salvage were measured longitudinally in 9 pregnant women throughout pregnancy and compared with those of 8 nonpregnant women (Table 2). Pregnancy was associated with a significant increase in daily habitual dietary nitrogen (protein) intake. Even though there was no significant difference in urea production between the pregnant and nonpregnant women, the amount of urea produced or excreted as a proportion of nitrogen intake was significantly lower in the pregnant women, the amount of urea produced or excreted as a proportion of nitrogen intake was significantly lower in the pregnant and nonpregnant women, compared with 7 nonpregnant women. After subjects fasted overnight, urea kinetics were quantified after a prime constant-rate infusion of a [¹⁵N₂]urea tracer.
The various components of this model can be quantified by using isotopic tracers of essential amino acids, ie, amino acids that are not synthesized in the body, such as leucine (34–36), lysine (35, 36), and phenylalanine (37). In the case of the commonly used isotopic tracer [1-13C]leucine, the tracer is infused in the plasma compartments. During isotopic steady state, the rate of appearance of leucine in the plasma is calculated by tracer dilution. Because leucine is deaminated to its intracellular ketoanalogue α-ketoisocaproic acid (KIC) and because intracellular KIC is the only source of plasma KIC, measurements of 13C enrichment of KIC have been used as a measure of intracellular appearance of leucine. Finally, it is assumed that leucine represents a fixed component of whole-body protein and therefore the rate of appearance of leucine can be used to calculate the rate of protein breakdown or proteolysis. Leucine has an additional advantage in that, during catabolism of KIC, decarboxylation of C-1 results in irreversible loss of the tracer. Therefore, the rate of appearance of tracer carbon in expired carbon dioxide can be used to quantify the irreversible loss of leucine and hence protein oxidation. In relation to pregnancy specifically, leucine is rapidly transported to the fetus and hence the measurements of whole-body leucine kinetics represent the sum of leucine kinetics in both the mother and the fetus. With the use of these methods, the fetal contribution cannot be separated from the total measurement. However, as will be discussed, the fetal contribution to these measurements is relatively small.

Using the [1-13C]leucine tracer, Denne et al (38) quantified the rate of appearance, oxidation, and nonoxidative disposal of leucine in 11 healthy pregnant women between 21 and 39 wk of gestation. The subjects were studied after a brief fast (≈17 h) (Table 3). Although plasma leucine concentrations were lower during pregnancy, the total rate of appearance of leucine (flux), an index of proteolysis, was similar in the pregnant and non-pregnant groups. However, the rate of appearance of leucine/kg body wt was significantly less in the pregnant group than in the nonpregnant group. Of note, there was no significant difference between groups in the rate of oxidation of leucine. The rate of excretion of urinary nitrogen was significantly lower in the pregnant group (38). There was no correlation between indicators of leucine kinetics, ie, turnover, oxidation, and advancing gestation. The interpretation of the leucine kinetics data in this study is difficult. An increased accretion of protein by the fetus and the mother during the third trimester of pregnancy would be expected to have been associated with an increased rate of protein (and therefore leucine) turnover. These data also point to the difficulty in estimating protein oxidation, at least in the fasting state, from the leucine oxidation data. Thompson and Halliday (39) longitudinally quantified whole-body protein metabolism in 6 healthy pregnant women by using a continuous infusion of [1-13C]leucine. In this study, there was no significant change in the rate of protein synthesis or breakdown/kg body wt or in the rate of irreversible loss of protein during pregnancy. However, a significant increase in protein turnover could be inferred when the data were expressed in relation to fat-free mass. These authors did not measure fat-free mass but used data from the literature for their computations. It can be concluded from these 2 studies of leucine turnover that there is no significant change in the weight-specific rate of protein or leucine turnover during pregnancy.

**TABLE 3**

<table>
<thead>
<tr>
<th>Leucine kinetics during pregnancy</th>
<th>Pregnant</th>
<th>Nonpregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucine (µmol/L)</td>
<td>94 ± 192</td>
<td>119 ± 25</td>
</tr>
<tr>
<td>Leucine flux (µmol·kg⁻¹·h⁻¹)</td>
<td>68.2 ± 7.0</td>
<td>81.7 ± 12.5</td>
</tr>
<tr>
<td>(mmol/h)</td>
<td>4.99 ± 0.60</td>
<td>5.25 ± 1.60</td>
</tr>
<tr>
<td>Leucine oxidation (µmol·kg⁻¹·h⁻¹)</td>
<td>8.5 ± 2.7</td>
<td>9.0 ± 2.0</td>
</tr>
<tr>
<td>(mmol/h)</td>
<td>0.61 ± 0.18</td>
<td>0.56 ± 0.12</td>
</tr>
</tbody>
</table>

1/× ± SD; n = 11. Data from reference 38.
2/Significantly different from nonpregnant (ANOVA): 2P < 0.05,
3/P < 0.01.
Two other studies used a [15N]glycine tracer to quantify whole-body protein and nitrogen turnover in human pregnancy (40, 41). These studies showed that calculated whole-body nitrogen flux was not significantly changed in the third trimester of pregnancy, although there was a small decrease in protein oxidation with advancing gestation.

**RELATION BETWEEN LEUCINE TRANSAMINATION AND UREA SYNTHESIS DURING PREGNANCY**

Because branched-chain amino acids (leucine, isoleucine, and valine) are the major source of nitrogen for ureogenic amino acids, we quantified previously the relation between branched-chain amino acid transamination and urea synthesis in healthy pregnant women (18). The isotope-tracer model used in those studies is shown in Figure 3. Originally described by Matthews et al (42) and applied to nonpregnant women, the model involves prime constant-rate infusion of l-[15N,1-13C]leucine. [15N,1-13C]Leucine labels the extracellular and intracellular leucine pools. Deamination of the tracer results in loss of 15 N and formation of [13C]KIC and reamination results in addition of an unlabeled nitrogen and formation of [13C]leucine. The isotopic enrichments of all 3 labeled compounds—[15N13C]leucine, [13C]leucine, and [13C]KIC—can be measured by gas chromatography–mass spectrometry. Because transaminations are near-equilibrium reactions and because [13C]KIC is the only source of [13C]leucine, the 13C isotopic enrichment of leucine and KIC should be similar. The measured enrichments of [13C]leucine and [13C]KIC were observed to be similar in in vivo studies so that [13C]KIC enrichments can be substituted for that of [13C]leucine. Thus, the model described for leucine can be resolved as follows. The dilution of the dilabeled [15N13C]leucine in plasma reflects the appearance of leucine from protein breakdown and that formed from reamination of KIC. Leucine carbon flux calculated from the enrichment of [13C]leucine or [13C]KIC predominantly reflects protein breakdown because leucine carboxyl carbon is not lost by leucine transamination to and from KIC. Hence, subtraction of carbon flux from nitrogen flux provides an estimate of the rate of reamination (X\textsubscript{N}) of KIC. The rate of decarboxylation of leucine (C) can be estimated directly from the appearance of 13C in expired carbon dioxide. Finally, the rate of deamination of leucine (X\textsubscript{O}) is calculated by adding the reamination and decarboxylation (X\textsubscript{O} = X\textsubscript{N} + C). The data for 6 pregnant women studied longitudinally through pregnancy by using this model are shown in Table 4. Seven healthy nonpregnant women were studied for comparison. The leucine nitrogen flux was lower in pregnant women during the first and third trimesters of pregnancy when compared with nonpregnant women. As before, there was no significant change in leucine carbon flux or in the rate of decarboxylation of leucine. The calculated X\textsubscript{O} and X\textsubscript{N} were significantly different from those in nonpregnant women.

**FIGURE 3.** Modeling of leucine metabolism using a [15N13C]leucine tracer. Double-labeled leucine tracer and mass spectrometry can be used to quantify the turnover rates of leucine nitrogen (Q\textsubscript{N}), leucine carbon (Q\textsubscript{C}), the rate of transamination (X\textsubscript{N}, X\textsubscript{O}), and decarboxylation (C). KIC, α-ketoisocaproic acid; B, proteolysis; S, protein synthesis; I, dietary protein; E, irreversible loss of nitrogen in urine and by other routes.

**TABLE 4**

<table>
<thead>
<tr>
<th>Leucine metabolism during fasting in pregnancy(^1)</th>
<th>Nonpregnant (n = 7)</th>
<th>Trimester 1 (n = 6)</th>
<th>Trimester 2 (n = 6)</th>
<th>Trimester 3 (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucine nitrogen turnover</td>
<td>166 ± 35</td>
<td>145 ± 26</td>
<td>162 ± 25</td>
<td>143 ± 8</td>
</tr>
<tr>
<td>Leucine carbon turnover</td>
<td>105 ± 13</td>
<td>106 ± 21</td>
<td>113 ± 22</td>
<td>111 ± 21</td>
</tr>
<tr>
<td>Rate of decarboxylation of leucine</td>
<td>18.2 ± 2.1</td>
<td>20.2 ± 6.7</td>
<td>18.4 ± 5.0</td>
<td>18.2 ± 6.1</td>
</tr>
<tr>
<td>Rate of reamination of KIC</td>
<td>61.4 ± 29.9</td>
<td>38.5 ± 13.3</td>
<td>49.0 ± 18.5</td>
<td>32.7 ± 19.9</td>
</tr>
<tr>
<td>Rate of deamination of leucine</td>
<td>79.6 ± 30.2</td>
<td>58.7 ± 14.2</td>
<td>67.4 ± 18.1</td>
<td>50.9 ± 15.7</td>
</tr>
</tbody>
</table>

\(^1\text{X ± SD. KIC, keto analogue α-ketoisocaproic acid. Data from reference 18.}\)
lower only in the third trimester of pregnancy than in the non-pregnant women (P < 0.05), although a change was evident early in gestation. Of interest, the authors observed a significant correlation between the rate of transamination of leucine and the rate of urea synthesis (18). These data and others suggest that pregnancy-related adaptation in maternal nitrogen metabolism is evident early in gestation, before any significant change in fetal nitrogen accretion occurs.

QUANTITATIVE CONTRIBUTION OF THE FETAL METABOLISM TO TOTAL MATERNAL-FETAL NITROGEN METABOLISM

In human studies, the contribution of the fetus to the overall whole-body measurements cannot be separated. However, the observed quantitative changes in maternal nitrogen and protein metabolism are likely to be minimally influenced by the quantitative nitrogen requirements of the fetus because the estimated fetal amino acid requirements of nitrogen for accretion and energy (oxidation) cannot explain the overall change in the mother’s nitrogen metabolism. First, the decrease in urea synthesis and in leucine nitrogen kinetics occurs before any significant fetal nitrogen accretion early in the first trimester. Second, leucine nitrogen turnover increases in the second trimester at a time of increase in fetal nitrogen accretion and then decreases in the third trimester at a time of continued increase in fetal amino acid metabolism. Estimates of amino acid balance across the umbilical circulation and estimates of nitrogen accretion and amino acid oxidation by the fetus in human studies suggest that fetal nitrogen uptake approximates 450 mg · kg

\[1 \times 1 \text{d}^{-1}\] of which 120 mg · kg

\[1 \times 1 \text{d}^{-1}\] represents nitrogen accretion by the human fetus (47). In relation to the whole-body weight of the mother, this represents a nitrogen uptake by the fetus of <1 mg · kg maternal body wt \[1 \times 1 \text{h}^{-1}\] and a urea production rate by the fetus of 0.2 mg · kg maternal body wt \[1 \times 1 \text{h}^{-1}\], a negligible amount compared with the estimates of whole-body urea nitrogen production during gestation.

In relation to individual amino acids, of the total amino nitrogen taken up by the fetus, glutamine, glycine, alanine, and branched-chain amino acids represent the largest proportion in sheep fetuses (47, 48). These amino acids also represent a significant component of nitrogen uptake by a human fetus (43). Several studies showed unique interorgan fluxes of serine–glycine and glutamine–glutamate in the sheep fetus as a possible mechanism of transfer of nitrogen from the placenta to the fetal liver (49–51). Whether such transfer also occurs in the human fetus is unknown. In addition, the effect of these fetal-placental interrelations on overall maternal amino acid metabolism is not known.

SUMMARY AND SPECULATIONS

On the basis of the data presented, the adaptation in maternal nitrogen metabolism can be summarized as shown in Figure 4. Human pregnancy data show a decrease in total \(\alpha\)-amino nitrogen, a lower rate of urea synthesis, and a lower rate of branched-chain amino acid transamination. It is speculated that these adaptive responses are aimed at overall conservation of nitrogen and increased protein synthesis. The exact mechanism of this adaptation is not known. It may, however, be related to pregnancy-induced resistance to insulin action (for glucose) that is evident early in gestation. Insulin resistance by decreasing glucose uptake could result in a decreased anaplerotic carbon flux into the tricarboxylic acid cycle. This would result in a decreased flux of nitrogen acceptors, eg, pyruvate and \(\alpha\)-ketoglutarate, the carbon precursor of major ureogenic amino acids alanine and glutamine, ultimately leading to decreased ureogenesis.

In summary, adaptive responses in nitrogen metabolism during pregnancy are aimed at nitrogen and protein accretion initially by the mother and later by the mother and the fetus. These changes are evident early in gestation before there is any significant increase in the mass of the conceptus and are characterized by 1) a decrease in urea production, 2) a decrease in plasma \(\alpha\)-amino nitrogen, 3) a lower rate of branched-chain amino acid transamination, and 4) an unchanged rate of weight-specific protein turnover per kilogram body weight.

REFERENCES