Amino Acid Metabolism during Starvation in Human Pregnancy

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ABSTRACT To evaluate the factors regulating gluconeogenesis in pregnancy, plasma amino acid levels were determined during the course of an 84–90 hr fast in physically healthy women studied during wk 16–22 of gestation (before undergoing therapeutic abortion), and in nonpregnant controls. The effect of pregnancy on the glycemic response to exogenous alanine administration during starvation was also investigated.

In the nonpregnant group fasting resulted in a 2- to 3-fold increase in the levels of plasma valine, leucine, isoleucine, and α-aminobutyrate, while the concentration of alanine and glycine fell. In the pregnant group, the levels of most amino acids were significantly reduced in the postabsorptive state. With starvation, the plasma concentration of alanine fell more rapidly in the pregnant group and was significantly below that of the nonpregnant subjects for the first 60 hr of the fast. In contrast, a significant elevation in plasma glycine, serine, and threonine was observed in the pregnant group after 84 hr of fasting, whereas similar increments were not demonstrable until after 10 days of fasting in previously studied nonpregnant obese subjects. Paralleling the changes in maternal plasma, amniotic fluid levels of valine, leucine, and isoleucine increased while that of alanine fell during the fast.

Although the plasma glucose concentration was lower in the pregnant group at termination of the fast, intravenous alanine administration (0.15 g/kg), resulted in a prompt, comparable increase (20–25 mg/100 ml) in plasma glucose in both groups of subjects.

It is concluded that (*a*) pregnancy accelerates and exaggerates the hypoalaninemic and hyperglycinemic effects of starvation; (*b*) lack of key endogenous substrate rather than altered intrahepatic processes may limit hepatic gluconeogenesis in pregnancy and contribute to gestational hypoglycemia; (*c*) maternal caloric deprivation profoundly alters the levels of amino acids in amniotic fluid.

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INTRODUCTION

The influence of human pregnancy in exaggerating and accelerating the blood glucose, insulin, and ketone response to caloric deprivation has recently been demonstrated in women fasted during the second trimester (1). One of the major problems raised by these and similar studies in experimental animals (2, 3), concerns the mechanism whereby gluconeogenesis is regulated in gestation. Specifically, the basis for the failure of maternal gluconeogenic processes to keep pace with the total glucose requirements of the conceptus and mother has not been established. Thus during the course of a 3–4 day fast, maternal blood glucose levels fall markedly (1, 4), while urea nitrogen excretion, reflecting hepatic gluconeogenesis (5), fails to increase above the levels observed in the nongravid state (1). This gestational exaggeration of fasting hypoglycemia occurs in the face of maternal hypoinsulinemia and hyperketonemia, conditions which would be expected to augment hepatic gluconeogenesis (6, 7). The question thus may be raised as to whether pregnancy directly alters intrahepatic processes or alternatively affects the supply of glucose precursors so as to limit hepatic glucose production.

With respect to possible direct effects of gestation on the liver, studies with isotopically labeled glucose precursors in the starved pregnant rat have revealed an augmented rather than diminished capacity for conversion of exogenous substrate to glucose (3, 8). Similar data are not however available in man. As to the role of endogenous substrate presentation, the importance of

the level of circulating alanine in the regulation of hepatic gluconeogenesis has been demonstrated in previous investigations in nonpregnant subjects fasted for prolonged periods (9). While data are available on the influence of pregnancy on plasma amino acid levels in the postabsorptive state (10–12) the effect of gestation on the amino acid response to starvation has not been examined. The significance of evaluating amino acid metabolism in the fasted pregnant state is underscored by the unique interaction which exists in this circumstance between maternal gluconeogenic mechanisms which require amino acids as glucose precursors, and placental transport processes which must meet fetal demands for amino acids for protein synthesis. Both processes thus are ultimately dependent on maternal protein stores and circulating amino acids as their source of substrate.

The present study was consequently designed to evaluate the factors regulating gluconeogenesis in human gestation by examining plasma amino acid levels in subjects fasted for 84–90 hr in mid-pregnancy. In addition, as an indication of possible direct effects of gestation on maternal gluconeogenic potential during starvation, the blood glucose response to exogenous alanine administration has been determined. Finally, inasmuch as amniocentesis has become a useful diagnostic technique in the prenatal diagnosis of genetic disorders (13, 14), and since fasting has been demonstrated to alter amniotic fluid levels of glucose and ketones (15), the effects of caloric deprivation on the concentration of amino acids in amniotic fluid has been investigated.

METHODS

Subjects (Table I). Two groups of pregnant volunteers ("fasted" and "fed", Table I) were studied during the second trimester. They were in good physical health, and had been legally approved to undergo therapeutic abortion for psychiatric reasons by means of transabdominal intra-amniotic installation of hypertonic saline. The nonpregnant group consisted of 11 healthy volunteers of similar age and weight (Table I). None of the pregnant or nonpregnant subjects had a history or evidence of obesity, diabetes, thyroid or adrenal disorders, or liver disease. They were informed of the nature, purpose, and possible risks of the study before giving their voluntary consent. In the case of the pregnant group, the subjects were informed that therapeutic abortion would be performed regardless of their participation in the study.

TABLE I
Clinical Data on Subjects

	Pregnant		
	Fasted	Fed	Nonpregnant
Number	17	6	11
Age, *yr*	15–26	15–21	19–23
Duration of pregnancy, *wk*	16–22	16–22	—
Body weight, *kg*	47–67	50–67	53–70
% Ideal weight*	94–107	96–107	90–113
Weight loss,‡ *kg*	3.3±0.2	—	3.1±0.4

* Based on Metropolitan Life Insurance tables, 1959.
‡ During the course of 84–90 hr of fasting.

Procedures. All of the subjects were hospitalized at the Clinical Research Center of the Yale-New Haven Hospital. 17 of the pregnant subjects and 7 of the nonpregnant subjects were studied during the course of an 84–90 hr fast. Starvation was initiated after completion of the evening meal at 8 p.m. on the day of admission and was continued for 84–90 hr, until the morning of the 5th hospital day. During this time intake was limited to 1200 ml (or more) of water per day. Blood samples were obtained from an antecubital vein between 8 and 9 a.m. on each day of the fast with the subjects in the recumbent position. Simultaneous samples of maternal venous blood and amniotic fluid were drawn from 12 of the pregnant subjects after completion of 84–90 hr of starvation, immediately before intra-amniotic installation of saline. Blood samples were drawn from four additional nonpregnant subjects after an overnight (12 hr) fast only.

L-Alanine was administered in a dose of 0.15 g/kg to five of the pregnant and five of the nonpregnant subjects on the morning of the 5th hospital day, after 84 hr of fasting. The alanine was infused intravenously over 3 min as a 10% sterile, pyrogen-free solution. Blood samples were obtained from an indwelling needle in an antecubital vein at intervals of 10–30 min for 30 min before, and for 180 min after completion of the alanine infusion.

The subjects in the "fed" pregnant group (Table I) were maintained on a 2200–2400 kcal diet. Simultaneous samples of maternal venous blood and amniotic fluid were collected 3–6 hr after ingestion of the breakfast meal immediately before intra-amniotic installation of hypertonic saline.

In both the fed and fasted groups the amniotic fluid was obtained percutaneously (via a spinal needle inserted through the abdominal wall under aseptic conditions), and was free of gross contamination by blood. To minimize further the possibility of contamination by maternal blood, the first 50 ml of amniotic fluid obtained was discarded; analyses were performed on the second 50 ml withdrawn.

Chemical analyses. For analysis of amino acids, heparinized plasma and amniotic fluid were deproteinized with sulfosalicyclic acid (16) immediately after collection. The supernates were stored at −20°C until analysis. Individual free amino acids were determined in the deproteinized supernates by the automated ion-exchange chromatographic technique (17). Glucose was measured in plasma by the glucose oxidase procedure (18).

Statistical analyses were performed according to the method of Snedecor (19). Data on blood glucose, insulin, and ketone acid levels and on urinary nitrogen excretion during the course of the fast in 12 of the pregnant and 6 of the nonpregnant subjects have been reported previously (1).

RESULTS

Nonpregnant subjects. In Table II the amino acid response to starvation is shown for the nonpregnant subjects. In accordance with previous studies in obese subjects (9), a 2- to 3-fold increment was observed in the branched-chain amino acids, valine, leucine, and iso-

TABLE II

*Plasma Amino Acid Levels during an 84 hr Fast in Nonpregnant Women**

	Duration of fast (hr)			
	12 (n = 11)	60 (n = 7)	84 (n = 7)	P‡
Taurine	51.5±2.5	57.9±3.4	48.9±6.6	NS
Threonine	138.0±11.3	98.7±2.5	111.4±10.0	NS
Serine	126.3±6.0	110.3±7.2	121.7±8.2	NS
Proline	151.3±10.1	141.3±10.0	152.6±9.7	NS
Citrulline	27.2±1.2	26.4±2.0	24.0±2.0	NS
Glycine	197.4±14.6	152.3±17.9	168.7±15.0	<0.05
Alanine	279.3±15.1	266.6±20.1	218.6±9.4	<0.02
α-Aminobutyrate	22.0±3.1	66.0±3.5	70.6±4.7	<0.001
Valine	201.4±11.7	410.4±34.0	407.6±36.4	<0.005
Cystine	94.8±5.4	109.0±5.0	99.8±5.6	NS
Methionine	18.0±1.7	21.7±1.4	21.4±1.3	<0.005
Isoleucine	51.4±2.7	151.6±11.4	155.7±9.8	<0.001
Leucine	99.5±2.0	266.1±23.9	260.6±20.9	<0.001
Tyrosine	40.4±3.3	53.4±5.6	51.3±4.4	<0.01
Phenylalanine	45.8±2.4	54.9±2.5	52.7±2.0	<0.02
Ornithine	71.8±7.6	—	53.8±4.6	<0.025
Lysine	164.1±12.1	—	141.8±13.4	<0.025
Histidine	81.4±5.5	—	74.7±4.8	NS
Arginine	55.5±6.6	—	43.8±3.0	NS

* Data are presented as mean±SE in μmoles/liter. The basic amino acids were not measured in the 60-hr samples.

‡ P = significance of difference between values observed after 12 and 84 hr of fasting (paired t test, n = 7).

TABLE III

*Plasma Amino Acid Levels during an 84 hr Fast in Pregnant Women**

	Duration of fast (hr)			
	12 (n = 12)	60 (n = 12)	84 (n = 12)	P‡
Taurine	36.0±2.9§	43.7±3.6	42.3±3.8	NS
Threonine	150.9±7.0	142.3±9.3	173.5±12.6	<0.05
Serine	107.4±4.6‖	128.2±5.6	132.7±6.1	<0.001
Proline	93.8±4.9§	104.4±4.1	124.8±6.2	<0.001
Citrulline	18.9±0.8§	17.0±0.6	17.2±0.9	NS
Glycine	120.8±7.6§	127.3±9.3	151.3±13.0	<0.005
Alanine	221.6±9.0¶	200.3±8.2	203.8±7.1	<0.05
α-Aminobutyrate	20.4±1.6	52.2±2.3	60.1±2.6	<0.001
Valine	169.8±3.9‖	337.2±12.0	333.5±17.0	<0.001
Cystine	69.1±3.0§	75.0±0.6	65.3±2.6	NS
Methionine	16.7±0.7	20.2±6.1	22.8±1.6	<0.001
Isoleucine	47.0±1.8	112.8±5.5	109.7±6.9	<0.001
Leucine	91.0±2.5‖	198.8±8.7	195.0±12.1	<0.001
Tyrosine	34.5±1.7	42.2±1.7	44.1±2.9	<0.005
Phenylalanine	42.3±1.1	49.3±1.4	49.7±2.4	<0.005
Ornithine	33.7±5.0§	—	33.0±2.7	NS
Lysine	175.8±13.9	—	153.0±13.9	NS
Histidine	100.7±5.7‖	—	79.7±5.3	<0.005
Arginine	51.0±7.6	—	53.8±7.9	NS

* Data are presented as mean±SE in μmoles/liter. The basic amino acids were not measured in the 60-hr samples.

‡ P = significance of difference between values observed after 12 and 84 hr of fasting (paired t test).

§ Significantly different from 12 hr value in nonpregnant group ($P < 0.001$ unpaired t test).

‖ Significantly different from 12 hr value in nonpregnant group ($P < 0.025$, unpaired t test).

¶ Significantly different from 12 hr value in nonpregnant group ($P < 0.005$, unpaired t test).

leucine and in α-aminobutyrate. Smaller increments were noted in phenylalanine, tyrosine, and methionine. In contrast, a significant decline was observed in the concentrations of the key endogenous glycogenic amino acids (9, 20) alanine and glycine. The magnitude of this decline was greatest for alanine. Small decrements in lysine and ornithine were also observed.

Pregnant subjects. The amino acid levels in the pregnant subjects after an overnight (12 hr), 60 hr, and 84 hr fast are shown in Table III. In the postabsorptive state (12 hr fast), the levels of 10 of 19 amino acids were significantly reduced below those observed in the nonpregnant group. The mean values of most of the remaining amino acids were also lower in the pregnant group though the changes were not statistically significant. Only in the case of histidine was the mean postabsorptive concentration significantly higher in the pregnant subjects.

In Fig. 1, plasma alanine levels are shown for the pregnant and nonpregnant subjects throughout the fast. Plasma alanine was significantly lower in the pregnant group in the postabsorptive state (12 hr fast) and for the first 60 hr of starvation. Furthermore, whereas a small but significant decline ($P < 0.05$) in plasma alanine occurred in the pregnant group between 12 and 60 hr of fasting, alanine levels failed to decline significantly in the nonpregnant group until 84 hr of starvation.

In Fig. 2 the changes in plasma glycine induced by starvation in pregnancy are compared with those observed in nonpregnant subjects and with the changes reported previously in nonpregnant obese subjects fasted for 10 days (9). In the nonpregnant group plasma glycine showed an initial decline and failed to rise above postabsorptive levels during the course of 84 hr of fasting. Similarly, in the obese nonpregnant group, an increment in plasma glycine above basal levels was not observed until after 10 days of starvation. In marked contrast,

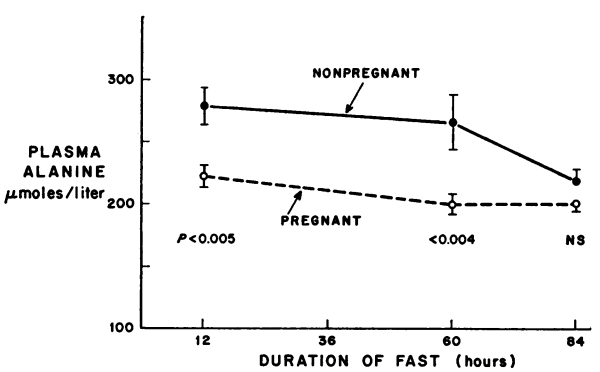

FIGURE 1 Plasma alanine levels in pregnant and nonpregnant subjects during the course of an 84 hr fast. (Mean ±SE). P values refer to significance of differences between pregnant and nonpregnant subjects.

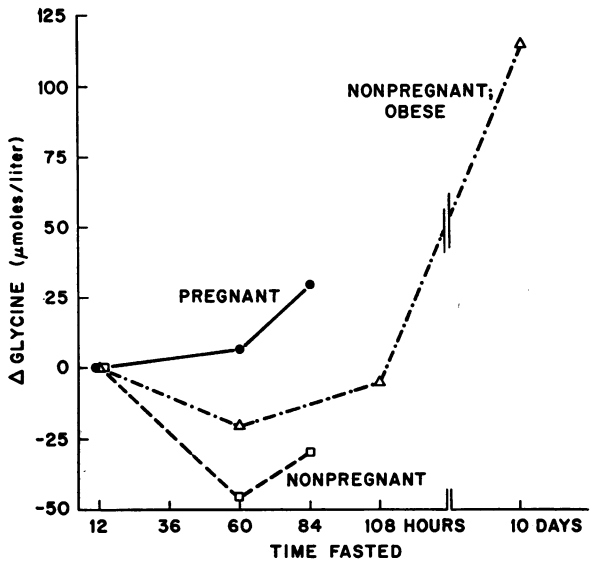

FIGURE 2 Changes in plasma glycine concentration during the course of an 84 hr fast in pregnant and nonpregnant subjects and in previously reported (9), prolonged fasted nonpregnant obese subjects. The mean changes from the basal, postabsorptive state (12 hr fast) are shown.

plasma glycine concentration began to rise within 60 hr of fasting in the pregnant group and was significantly elevated by 84 hr. A similar acceleration was observed in the pregnant group with respect to starvation-induced increases in plasma threonine and serine. Whereas the concentration of these amino acids failed to rise above basal levels during 84 hr of fasting in the nonpregnant group (Table II), and required 5–10 days of fasting to become elevated in the prolonged fasted obese group (9), a significant elevation was observed after 60–84 hr of caloric deprivation in pregnancy (Table III).

The response of the branched-chain amino acids and α-aminobutyrate was generally similar to the nonpregnant group. However, the absolute rise in leucine and isoleucine was smaller in the pregnant group (Table III). Elevations were also observed in methionine, tyrosine, and phenylalanine.

The influence of starvation on amino acid levels in amniotic fluid is shown in Table IV. The concentration of the branched-chain amino acids and α-aminobutyrate increased markedly, while alanine levels fell by 25%. Small increments in taurine and serine were also demonstrated. Despite the changes in amino acid levels in amniotic fluid, the relation between amniotic fluid and maternal plasma amino acid concentrations was generally not altered by starvation. Thus the ratios of amniotic fluid to maternal plasma concentrations did not differ in the fed and fasted groups for most amino acids (Table IV). Small decreases were noted however, after fasting in the case of glycine and methionine.

Response to alanine. The effect of alanine administration on plasma glucose levels during prolonged starvation is shown in Fig. 3. Before alanine infusion, plasma glucose concentration after 84 hr of starvation (−10 and 0 values, Fig. 3) was, as anticipated (1), significantly lower in the pregnant group ($P < 0.05$). However, after alanine administration, a comparable increase in plasma glucose was observed in the pregnant and nonpregnant subjects (Fig. 3). In both groups plasma glucose levels rose within the first 10 min, reaching a peak at 50 min. The mean (±SE) maximal increase in plasma glucose was 21.2±2.0 mg/100 ml in the nonpregnant group and 24.6±1.0 mg/100 ml in the pregnant subjects.

DISCUSSION

Previous studies on the amino acid response to starvation in the nonpregnant state have dealt exclusively (9), or primarily (21) with obese individuals. The current data in the nonpregnant group thus provide evidence that the increase in branched-chain amino acids and fall in glycogenic amino acids induced by starvation is not a consequence of the obese state. Furthermore, since the specific amino acids which increased in both the nonpregnant and pregnant groups (valine, leucine, isoleucine, α-aminobutyrate, phenylalanine, and tyrosine) correspond to those amino acids which are uniquely sensitive to changes in endogenous insulin levels (22)

TABLE IV

*Influence of Fasting on Amino Acid Levels in Amniotic Fluid and on the Ratio of Amniotic Fluid to Maternal Plasma (AF:MP) Amino Acid Concentrations**

	Amniotic fluid			AF:MP	
	Fed‡	Fasted§	P‖	Fed‡	Fasted§
Taurine	77.2±5.4¶	98.9±7.8	<0.05	2.4	2.3
Threonine	197.7±28.2	173.7±14.2	NS	1.2	1.0
Serine	33.5±3.4	42.9±2.6	<0.05	0.3	0.3
Proline	175.2±12.9	159.9±9.7	NS	1.5	1.3
Citrulline	12.0±0.5	8.1±1.5	<0.02	0.6	0.5
Glycine	169.8±18.2	151.9±11.6	NS	1.4	1.0
Alanine	353.0±21.5	264.8±17.1	<0.005	1.4	1.3
α-NH_2 butyrate	13.4±2.7	52.7±2.3	<0.001	0.9	0.9
Valine	136.2±9.4	255.3±18.2	<0.001	0.8	0.8
Cystine	77.8±8.0	72.8±4.1	NS	1.1	1.1
Methionine	19.2±2.0	20.3±1.4	NS	1.2	0.9
Isoleucine	23.8±3.1	68.3±5.3	<0.001	0.5	0.6
Leucine	51.7±5.1	133.4±11.0	<0.001	0.6	0.7
Tyrosine	43.7±1.8	46.6±3.6	NS	1.2	1.1
Phenylalanine	48.5±1.9	52.2±3.4	NS	1.2	1.1

* The basic amino acids were not measured in the amniotic fluid samples.
‡ Amniotic fluid and maternal plasma were obtained 3–6 hr after the previous meal in subjects maintained on a 2200–2400 kcal diet (n = 6).
§ Amniotic fluid and maternal plasma were obtained after 84–90 hr of fasting (n = 12).
‖ P = significance of differences between mean values in fed and fasted groups (unpaired t test).
¶ Mean±SE, μmoles/liter.

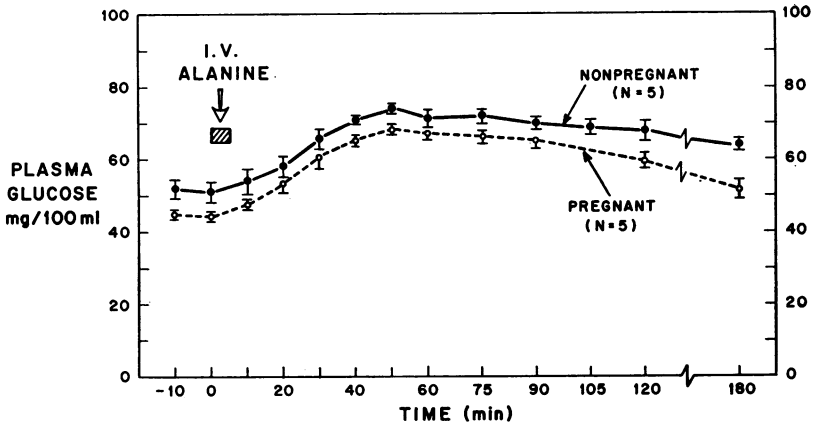

FIGURE 3 Plasma glucose response to intravenous administration of alanine (0.15 g/kg) after 84 hr of starvation in pregnant and nonpregnant subjects. Before alanine administration (−10 and 0 min), the glucose levels were significantly lower ($P < 0.05$) in the pregnant group.

and to administration of exogenous insulin (23), the current findings support the conclusion advanced elsewhere (9), that the hyperaminoacidemia of starvation is a consequence of the hypoinsulinemia.

The findings in the pregnant group are of interest with respect to the basal postabsorptive state as well as with regard to the observations during the course of the fast. Although it has long been recognized that pregnancy is characterized by hypoaminoacidemia (24), most of the data on plasma levels of individual amino acids have been obtained on subjects studied in the third trimester (11), often at the time of delivery (25). Little information is available regarding amino acid concentrations at earlier stages of pregnancy (10). Young and Prenton (12) measured maternal plasma amino acid levels in six patients during wk 16–19 of gestation immediately before delivery of the fetus by hysterotomy. Since their patients were anesthetized and in the midst of a surgical procedure the conditions of their study were considerably different from those of the present investigation. The current data indicate that in physically healthy, unanesthetized women, a significant reduction in the postabsorptive levels of most amino acids occurs by wk 16–20 of gestation. In accordance with these findings in humans are recent observations in subhuman primates, in whom gestational hypoaminoacidemia is manifest by midpregnancy with no further reduction in amino acid levels occurring as pregnancy progresses to term (26). The unique increase in postabsorptive levels of histidine in the pregnant group is in keeping with previous demonstrations of relative or absolute hyperhistidinemia during late pregnancy in women (25), and in monkeys studied at various stages of gestation (26).

The effect of pregnancy on the concentration of plasma alanine during starvation is of particular importance since this amino acid has been identified as the primary endogenous glycogenic substrate released by muscle (27, 28) and extracted by the liver (9, 20, 29). In addition, a reduction in plasma alanine has been demonstrated to be of primary importance in the limitation of hepatic gluconeogenesis during prolonged starvation in nonpregnant subjects (9). The current observation that pregnancy accelerates and exaggerates the hypoalaninemic response to starvation suggests that substrate lack contributes to the fasting hypoglycemia characteristic of pregnancy. Lack of endogenous circulating alanine thus may be responsible for the failure of hepatic gluconeogenesis to increase adequately to maintain euglycemia in the face of combined maternal and fetal requirements for glucose. It is noteworthy in this respect that the effect of pregnancy in lowering plasma alanine levels occurs during the first 60 hr of starvation and is coincident with the period in which the exaggerated decline in plasma glucose is most pronounced (1). A similar deficiency in endogenous glycogenic substrate has recently been reported in the fasted pregnant rat (30). In addition, hypoalaninemia comparable to that observed in the pregnant group has been demonstrated to be of primary pathogenetic significance in the syndrome of ketotic hypoglycemia of infancy (31).

Further evidence that lack of glucose precursors rather than altered intrahepatic events is responsible for gestational hypoglycemia is provided by the plasma glucose response to administration of exogenous alanine. When plasma alanine levels were increased in the pregnant group by intravenous infusion of this amino acid, a prompt hyperglycemic response was observed (Fig. 3). Furthermore, despite the lower initial fasting plasma glucose concentrations in the pregnant group, the rapidity with which plasma glucose levels increased and the peak

increments achieved were equivalent to those observed in the nonpregnant subjects. These findings support the conclusion that maternal hepatic gluconeogenic mechanisms are capable of responding to increased substrate delivery during starvation in pregnancy.

Since alanine has been demonstrated to stimulate glucagon release (32), the question may be raised as to whether glycogenolysis rather than increased gluconeogenesis is responsible for the glycemic response to alanine. That such is not the case in subjects fasted 3–4 days is suggested by the data of Hultman and Nilsson who demonstrated virtually complete depletion of hepatic glycogen reserves during the first 24–48 hr of starvation (33). In addition, studies with isotopically labeled alanine in the overnight and prolonged fasted state have demonstrated that alanine-^{14}C is promptly incorporated into blood glucose (34).

As to the mechanism of the hypoalaninemia in pregnancy, aminoaciduria has been well documented in gestation (11). However, in contrast to many other amino acids, renal clearance of alanine does not increase in early pregnancy (10). Nevertheless, altered renal handling of alanine during starvation in early pregnancy cannot be excluded on the basis of the current data. Diminished alanine output from maternal protein stores or increased hepatic extraction of alanine could also result in a diminution in circulating levels of this amino acid. However, the former would be expected to result in a reduction and the latter in an augmentation in hepatic gluconeogenesis. The failure to observe any significant difference between pregnant and nonpregnant subjects in the rate of urea nitrogen excretion during starvation (1), supports neither hypothesis. A further possibility is that continuous uptake of alanine by the placenta in the face of preferential utilization of this amino acid for maternal hepatic gluconeogenesis results in depletion of the circulating levels of this substrate. Supporting such a mechanism is the demonstration that active transport of amino acids by the placenta is at least as pronounced in early gestation as in the later stages of pregnancy (25). Accordingly, maternal hypoglycemia, initiated by augmented glucose utilization consequent to fetal dependence on glucose as its primary metabolic fuel (1–3), may be perpetuated by the conceptus' siphoning of glycogenic precursors as well.

The influence of pregnancy on the changes in plasma glycine, threonine, and serine during fasting are of interest inasmuch as these amino acids are unique in demonstrating a delayed increase during prolonged starvation of obese nonpregnant subjects (9). The accelerative effect of pregnancy on the amino acid response to starvation is indicated by the elevations in these amino acids within 60–84 hr of fasting in the pregnant group. As to the mechanism of this increment, hyperglycinemia has been reported in protein-calorie malnutrition (35), and in the mother and neonate in association with restricted maternal protein intake (36). This association of hyperglycinemia with protein lack raises the possibility that the accelerative action of pregnancy on the plasma glycine response to fasting may be a consequence of more rapid depletion of maternal protein reserves resulting from continuous placental transport of amino acids to meet fetal requirements for protein synthesis.

The concentrations of amino acids in amniotic fluid were investigated inasmuch as amniocentesis has been suggested as a useful technique in the antenatal diagnosis of inherited abnormalities of amino acid metabolism and other genetic disorders (13, 14). While it is generally advantageous to establish such diagnoses at an early stage of pregnancy the limited quantitative data available on amino acid levels in amniotic fluid have generally been obtained at term (37, 38). The current findings in the fed group (Table IV) thus may constitute a useful base line for future comparisons in the prenatal detection of amino acid disorders. Of possibly greater interest is the clear-cut effect of starvation on amino acid levels in amniotic fluid as indicated by a marked increase in valine, leucine, and isoleucine and a decrease in alanine. That these changes were a consequence of altered maternal amino acid levels rather than a result of starvation-induced effects of transport processes in the conceptus is suggested by the generally unaltered ratios of amniotic fluid to maternal plasma amino acid concentrations (Table IV). Moreover the changes in amniotic fluid were restricted to those amino acids demonstrating the greatest absolute perturbations in maternal plasma cencentration during the course of the fast. Regardless of the mechanism involved, the current data indicate that the levels of amino acids in amniotic fluid are profoundly influenced by maternal nutrition. Accordingly, consideration must be given to the preexisting nutritional status of the mother in the antenatal diagnostic evaluation of amino acid concentrations in amniotic fluid.

It should be noted that the column chromatographic technique employed in the current study precluded accurate measurements of glutamine and glutamate (39). The importance of glutamine as a renal substrate is well established (40), while more recent studies have demonstrated muscle release and hepatic uptake of glutamine in postabsorptive man (41). An increase in renal ammoniagenesis and presumably in renal gluconeogenesis has been demonstrated during starvation in pregnancy (1). Whether changes in glutamine metabolism contribute to the altered pattern of gluconeogenesis in pregnancy remains to be determined.

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