Maternal and fetal fuel homeostasis in human pregnancy\textsuperscript{1, 2, 3}

Philip Felig, M.D.

The interaction of maternal and fetal metabolism in normal pregnancy constitutes a unique situation with regard to fuel homeostasis. Continuous consumption of energy-yielding substrates by the fetus and the production of hormones by the placenta markedly alter the metabolic milieu in the maternal circulation. Simultaneously, the pattern of substrate delivery across the placenta and the enzymatic development in the fetus determine the profile of metabolic fuel consumption by the conceptus. It is the purpose of this report to review recent studies on fuel metabolism in pregnancy as gleaned from observations on physically healthy women fasted for 84 to 90 hr in mid-gestation (1-4).

Although a number of investigators have examined both the maternal (5, 6) and fetal (7, 8) response to fasting in pregnant rats and sheep (9), previous observations in humans had been limited to the postabsorptive or overnight fasted condition (10, 11). The availability of a group of physically healthy women undergoing therapeutic abortion for psychiatric reasons in weeks 16 to 22 of gestation provided the first opportunity to examine the metabolic response to fasting in human pregnancy (1). The resultant observations have not only expanded our knowledge regarding fuel homeostasis, but also have implications regarding nutritional management in pregnancy.

\textit{Maternal glucose, insulin, and ketone levels}

After an overnight fast and throughout the course of 4 days of fasting, plasma glucose levels are significantly lower in pregnant than in nonpregnant women (Fig. 1). The prevalence of fasting hypoglycemia in the pregnant group is underscored by the individual glucose values at completion of the fast. Whereas plasma glucose fell below 50 mg/100 ml in only one of six nonpregnant controls, glucose levels below 50 mg/100 ml were observed in eight of the pregnant subjects. That pregnancy accelerated as well as exaggerated the response to fasting is evident from the fact that the plasma glucose concentration reached a plateau within 36 hr in the pregnant group but was still declining at 84 hr in the nonpregnant subjects.

The effect of pregnancy on the response of plasma insulin to fasting is similar to that observed with glucose (Fig. 2). After an overnight fast and for the first 60 hr of fasting, plasma insulin in the pregnant women was reduced to approximately 50% of the concentration observed in the nonpregnant controls. Furthermore, whereas plasma insulin reached its nadir in the pregnant group within 36 hr, in the nonpregnant subjects a continuous decline was observed over 84 hr before comparable levels were reached.

To determine the basis of the hypoinsulinemia during fasting in mid-pregnancy, the relation between plasma insulin and glucose was examined. In both the pregnant and nonpregnant groups, plasma insulin showed a significant direct linear correlation with plasma glucose (Fig. 3). The data are consistent with the conclusion that the hypoinsulinemia in the pregnant group is a consequence of the hypoglycemia.

As a number of investigators have reported

\textsuperscript{1} From the Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut 06510.

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\textsuperscript{4} Associate Professor of Medicine and Director, General Clinical Research Center, Yale University School of Medicine.
hyperinsulinemia in pregnancy (10, 11), the above data may seem at variance with established concepts. However, two aspects of the fasting data need be emphasized. Firstly, we are dealing with basal rather than glucose-stimulated or aminogenic-stimulated insulin concentrations. Thus, although the stimulative response of the beta cell increases with pregnancy, basal secretion falls in association with the fall in basal glucose levels (12). Secondly, the fasting studies were conducted at 16 to 22 weeks of gestation, well before the marked increase in insulin responses observed in the third trimester (10, 13).

The influence of pregnancy on ketosis during fasting is shown in Fig. 4. After an overnight fast and for the first 36 to 60 hr of starvation, blood β-hydroxybutyrate and acetoacetate were two- to threefold higher in the pregnant group. This augmentation in fasting ketosis in the pregnant group was, however, not apparent throughout the fast. At 84 hr, and in association with equalization of plasma insulin levels, blood ketone levels became virtually identical in the two groups of subjects. Ketone acid concentration thus was higher in the pregnant group only as long as plasma insulin levels were significantly below those of nonpregnant controls. The data thus suggest that hypoinsulinemia is responsible for the heightened ketonemia of pregnancy. This effect of insulin lack is likely to be mediated via augmented lipolysis.

The maternal response to fasting with re-

![Fig. 1. Plasma glucose concentration in pregnant and nonpregnant subjects during an 84-hr fast (based on the data of Felig and Lynch (1)).](image1)

![Fig. 2. Plasma insulin levels during an 84-hr fast in pregnant and nonpregnant subjects (1).](image2)

![Fig. 3. Relation between plasma insulin and glucose during an 84-hr fast in nonpregnant and pregnant subjects (based on the data of Felig and Lynch (1)).](image3)
spect to circulating fuels and insulin thus may be characterized as an exaggeration and acceleration of the phenomena observed in the nongravid condition. Glucose concentration falls more rapidly and to a greater extent thereby causing hypoinsulinemia which, in turn, precipitates an augmentation in ketosis during fasting.

**Maternal gluconeogenesis and amino acid metabolism**

Of particular interest is the mechanism responsible for the striking degree of fasting hypoglycemia observed in the pregnant group. Possible explanations include increased glucose consumption by the fetus and failure to adequately increase maternal glucose production. With respect to the latter, body glycogen stores (approximately 70 g) are inadequate to meet cerebral glucose requirements for even 24 hr (14, 15). Maintenance of glucose homeostasis consequently depends in part on intact mechanisms of protein catabolism and gluconeogenesis. Breakdown of body protein in fasting is reflected in the rate of urinary nitrogen loss. In addition, balance studies during prolonged fasting have demonstrated that the rate of hepatic gluconeogenesis is reflected in urinary urea excretion, whereas renal gluconeogenesis is directly related to urine ammonia loss (16).

The influence of pregnancy on urinary excretion of total nitrogen, ammonia, and urea during fasting is shown in Fig. 5. Total nitrogen excretion was slightly increased on days 1 and 2 of the fast and was significantly elevated in the pregnant group on day 3. This increase was due to an elevation in urinary ammonia excretion, which rose to levels twice those observed in nonpregnant controls on day 2 and 3. Because the level of ketones in blood and urine determines the rate of ammonia excretion (6, 16), hyperketonemia is the likely explanation for the heightened excretion of ammonia in the gravid state. Regardless of the mechanism of the increase in urinary ammonia loss, it is clear from the elevation in total nitrogen excretion that fasting hypoglycemia in pregnancy occurs in the face of accelerated maternal protein catabolism. Moreover, in view of the interdependence of renal ammoniagenesis and gluconeogenesis (16, 17), the elevation in urinary ammonia excretion is consistent with an augmentation in renal gluconeogenesis in the pregnant group. The data thus do not support an overall decline in maternal glucose production from protein precursors, but point to augmented glucose utilization, presumably by
the conceptus, as at least a contributing factor in the development of maternal hypoglycemia.

Despite the overall increase in protein catabolism and presumably in renal gluconeogenesis, it is clear that total maternal (hepatic + renal) gluconeogenic processes fail to keep pace with peripheral (maternal + fetal) glucose requirements as reflected by the fall in blood glucose. In this regard, the changes in urea excretion are of particular interest. In contrast to the response in urine ammonia, urinary urea excretion failed to increase significantly above the levels observed in nonpregnant subjects (Fig. 5). In view of the hypoinsulinemia and accelerated ketosis in the pregnant group, factors that normally enhance hepatic gluconeogenesis (15), increased urea production might have been anticipated in the gravid state. The question thus may be raised as to whether maternal hepatic gluconeogenesis is limited in pregnancy as a consequence of alterations in intrahepatic processes or alternatively as a result of changes in the supply of glucose precursors.

Concerning possible direct effects of gestation on the liver, studies in pregnant rats involving isotopically labeled glucose precursors have revealed an augmented rather than diminished capacity for conversion of exogenous substrate to glucose (6, 18). However, similar data are neither available nor readily obtainable in humans. As to the role of endogenous substrate presentation, previous studies have identified alanine as the key gluconeogenic precursor (19, 20). Furthermore, in prolonged fasting, alanine availability is the rate-limiting factor in hepatic gluconeogenesis (21).

As shown in Fig. 6, plasma alanine concentration was significantly lower in the pregnant group in the postabsorptive state (12-hr fast) and for the first 60 hr of fasting. Furthermore, whereas a small but significant decline 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 fasting. The data thus indicate that pregnancy accelerates and exaggerates the hypoalaninemic response to fasting and suggest that lack of endogenous substrate contributes to gestational hypoglycemia. Further support for this conclusion is obtained from the glycemic response to infusion of alanine. When plasma alanine levels are increased in the pregnant group by intravenous infusion of this amino acid, a prompt increase in blood glucose (comparable to nonpregnant subjects) is observed (3).

With respect to the mechanism of hypalaninemia in pregnancy, significant urinary losses are unlikely to occur in early to midpregnancy (22). Diminished output of alanine from maternal protein stores is possible, but one would anticipate an absolute decline in urinary urea excretion if net protein catabolism were diminished. An alternative possibility is that uptake of alanine by the placenta (for transport to the fetus) in the face of preferential utilization of this amino acid for maternal gluconeogenesis results in depletion of the circulating levels of this substrate. By this formulation, maternal hypoglycemia, initiated by augmented glucose utilization consequent to fetal dependence on glucose as its primary metabolic fuel (23), may be perpetuated by the conceptus’ siphoning of glycogenic precursors as well.

**Chorionic somatomammotropin (HCS) secretion**

In view of the profound changes observed in maternal fuel metabolism during fasting, the question arises as to whether the secretion of placental hormones is influenced by the fasting condition. Of particular interest is the response of chorionic somatomammotropin (human placental lactogen), a placental polypeptide hormone which has been postulated to accelerate maternal lipolysis and en-
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![Graph](https://academic.oup.com/ajcn/article-abstract/26/9/998/4695331)

**Fig. 7.** Influence of fasting on plasma concentration of human chorionic somatomammotropin (HCS). P values refer to significance of changes from baseline (12 hr) observations (based on the data of Kim and Felig).  

Enhance amino acid availability to the conceptus (24). In previous studies, acute alterations in the concentration of glucose or amino acids in the maternal circulation failed to alter maternal plasma HCS levels. Consequently, changes in placental mass rather than alterations in the metabolic milieu had been considered the sole determinant of HCS secretion (24).  

In Fig. 7, the influence of fasting on maternal plasma HCS levels is shown. Although HCS concentration was unchanged for the first 36 hr, by 60 hr a 30 to 40% increase was observed. Examination of individual responses revealed that HCS levels rose in 13 of 14 patients studied (2). Similar data have been reported by Tyson (25).  

In view of the lipolytic and anabolic actions of HCS (24), increased secretion of this hormone may contribute to the augmented fasting ketosis of pregnancy and to limitation of maternal hepatic gluconeogenesis by promoting transfer of amino acids to the fetus. Although the mechanism of the elevation in plasma HCS remains to be determined, the data indicate that HCS secretion is influenced by nutritional deprivation and may not be governed solely by placental mass.

**Response of the conceptus to fasting**  
Because both pregnant and nonpregnant women tolerated the 84-hr fast quite well, the marked changes in metabolic fuels and hormones described above are of importance primarily to the extent to which they influence fetal metabolism. In the subjects studied, examination of fetal blood was not possible because therapeutic abortion was induced by intraamniotic installation of hypertonic saline resulting in fetal maceration. This procedure did, however, permit the examination of amniotic fluid withdrawn prior to saline injection (4).  

In Fig. 8, the concentrations in amniotic fluid of glucose, total ketone acids (β-hydroxybutyrate and acetoacetate), and free fatty acids are shown. The data in the patients fasted for 84 to 90 hr are compared with a “fed” group in whom amniotic fluid was withdrawn 3 to 6 hr after meal ingestion (4). The results indicate that in association with maternal hypoglycemia, amniotic fluid glucose fell to levels 40% below that in control subjects. Ketone acid concentration in amniotic fluid increased 40-fold above the level in the fed state and was comparable to maternal blood. In contrast, the concentration of free fatty acids remained unchanged in amniotic fluid, despite a marked increase in maternal levels (4). The latter finding is in keeping with the evidence of limited transport of FFA across the placenta (26, 27).  

The changes in amniotic fluid therefore suggest that fasting results in a diminution in the availability of glucose and an increased supply of ketones to the conceptus. As keto-
genesis by the fetal liver is quite limited (28), the ketones available to the conceptus during maternal fasting are more than likely derived from the maternal circulation by transfer across the placenta. Supporting this conclusion is the direct linear correlation between maternal and amniotic fluid concentrations of \( \beta \)-hydroxybutyric acid and acetoacetic acid (4).

The significance to fetal fuel metabolism of the fast-induced increases in ketone acids and diminution in glucose on the fetal side of the placenta can be determined only by direct measurements of extraction ratios across the umbilical vessels. Such data are not available in fasted humans. Nevertheless, on the basis of a number of recent observations on fetal metabolism in humans as well as experimental animals, a hypothesis may be advanced regarding fuel metabolism in fasting. A significant uptake of ketone bodies has been observed in the human fetus at delivery (27, 29). Furthermore, the enzymes necessary for ketone oxidation have been demonstrated in fetal brain tissue in humans (30) as well as rats (8). In fasted pregnant rats, blood ketones in the fetus increase to levels comparable to the maternal concentration, whereas fetal glucose levels show a prompt decline (8). Accompanying the fasting-induced hypoglycemia, a decrease in fetal glucose consumption has been observed in the pregnant ewe (9). Despite a relative abundance of liver glycogen in the fetus, fasting (in the rat) fails to result in mobilization of fetal hepatic glycogen stores (8). Finally, the activity in human fetal liver of key enzymes involved in glycogenolysis and gluconeogenesis (particularly phosphoenolpyruvate carboxykinase) is only 10 to 30% of that observed in the adult (31, 32).

Based on the above data, it is likely that fetal blood glucose levels fall and ketone acids rise in association with maternal fasting. Diminished availability of glucose from the maternal circulation and failure to mobilize fetal glycogen stores results in a decreased uptake of glucose by various fetal tissues. In contrast, hyperketonemia in the fetus is likely to be accompanied by augmented consumption of \( \beta \)-hydroxybutyrate and acetoacetate by fetal tissues, particularly the developing brain. The fetal adaptation to fasting thus may be considered analogous to the situation occurring in the human brain in the fasted adult, in which case, ketone acids replace glucose as important energy-yielding substrates (33). The similarity between the fetus and the adult brain applies to the fed state as well because, in that circumstance, glucose is the obligate fuel for both tissues and its uptake by these tissues is not dependent on maternal insulin secretion.

Summary of maternal–fetal–placental fuel–hormone interactions

The data obtained in human subjects in mid-pregnancy reveal an acceleration and exaggeration of the maternal fuel–hormone response to fasting. In addition, substrate availability to the conceptus and placental HCS secretion is profoundly altered by nutritional deprivation. The postulated interactions between these hormonal and substrate responses are shown in Fig. 9. Continuous glucose utilization by the fetus results in maternal hypoglycemia. Maternal insulin levels are consequently reduced, resulting in acceleration of fasting ketosis. The accompanying ketonuria increases renal ammonia production, which is presumably accompanied by an increase in renal gluconeogenesis. Maternal hypoaminoacidemia, particularly with respect to alanine, caused perhaps in part by fetal amino acid utilization for protein synthesis, acts to limit hepatic gluconeogenesis. Failure of acceleration of hepatic gluconeogenesis despite maternal hypoinsulinism contributes
further to maternal hypoglycemia. The changes in metabolic fuels in the maternal circulation alter substrate availability to the conceptus manifested by diminished glucose levels and hyperketonemia. Ketones may in turn become an important metabolic fuel for the fetus as glucose consumption by the conceptus diminishes. Finally, the placental response to caloric deprivation as evidenced by increased secretion of HCS may influence maternal and fetal metabolism by enhancing maternal lipolysis and fetal uptake of amino acids.

**Clinical implications**

There is currently much controversy as to the precise role of maternal nutrition in determining fetal birth weight and development. Some authors argue strongly that improvement in maternal nutrition is likely to reduce the incidence of low birth weights, particularly in impoverished and underdeveloped areas (34). In contrast, others, noting that even severe restrictions in food supply in Leningrad and Holland during World War II resulted in no more than a 5 to 10% reduction in birth weight, have minimized the importance of nutritional deprivation in fetal homeostasis (35). The relatively high ratio of maternal to fetal weight in humans as compared with experimental animals has been suggested as the basis of this seeming protection of the human fetus from the vagaries of maternal food intake (36). On the other hand, Churchill and Berendes recently reported that noninsulin dependent acetonuria occurring during pregnancy (presumably as a result of fasting) is associated with a significantly lower IQ in the offspring than in a matched control group without acetonuria (37). The impairment in intelligence occurred despite the fact that birth weights in the offspring of the acetonuric mothers were not significantly reduced.

Current obstetrical practice in the United States involves a great deal of emphasis on restriction of weight gain in pregnancy (38). The data reviewed above have demonstrated that ketonemia in pregnancy is three times greater than in the nonpregnant state after an overnight fast, and increases at an accelerated rate as fasting extends beyond 12 hours. Furthermore, it is likely that ketone acids are taken up by the fetus and replace glucose as energy-yielding substrates. To the extent that maternal ketosis may adversely influence fetal metabolism and development, the data suggest that severe caloric restriction should not be undertaken in pregnancy. Particularly to be avoided are weight reduction programs involving a severely limited intake of carbohydrate. Thus, the tendency on the part of some pregnant women to follow a "crash, starvation diet" to make up for previous, excessive weight gain, should be unequivocally condemned.

**References**

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