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Hazards associated with pregnancies and deliveries in lysinuric protein intolerance

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Abstract

Lysinuric protein intolerance (LPI) is an autosomal recessive transport disorder of the dibasic amino acids. The defect leads to deficiency of lysine, arginine, and ornithine and, secondarily, to a functional disorder of the urea cycle. Transient postprandial hyperammonemia and subsequent persistent protein aversion, linked with several other biochemical and clinical characteristics of the disease, suggest an increased risk for maternal and fetal complications during pregnancy and delivery. Our unique material on the outcomes of 18 pregnancies of 9 Finnish mothers with LPI and the follow-up of their 19 children shows that maternal LPI is truly associated with increased risk of anemia, toxemia, and intrauterine growth retardation during pregnancy and bleeding complications during delivery. Successful pregnancies and deliveries can still be achieved with careful follow-up of blood pressure and laboratory values. The children of the mothers with LPI generally develop normally. Special care of maternal protein nutrition and control of ammonemia, anemia, and toxemia during pregnancy are essential. We propose centralization of deliveries to obstetric units with capability to deal with bleeding complications and rare inborn errors of metabolism.

1. Introduction

Lysinuric protein intolerance (LPI; OMIM 222700), an autosomal recessive defect in the transport of cationic amino acids, was first described by Perheentupa and Visakorpi [1] in 1965 in children with failure to thrive, postprandial hyperammonemia, and protein aversion. Although there has been considerable progress in understanding the transport defect and genetics of LPI, our knowledge of the natural history of the disease is only gradually increasing, as follow-up data on this rare disease are accumulating. LPI is caused by mutations in the SLC7A7 (solute carrier family 7, member 7) gene encoding y^+LAT-1 (y^+L amino acid transporter 1) protein that combines with 4F2hc in endoplasmic reticulum (4F2 heavy chain) to form a functional heterodimeric transporter [2,3]. The transport defect in LPI is located at the basolateral membrane of the polar epithelial cells in the intestine and kidney tubuli [4,5]. Almost half of the more than 100 reported patients are of Finnish origin [6]. All Finnish patients with LPI share the same founder mutation 1181-2A →T (LPI_{Fin}) not found in patients with LPI elsewhere [7], albeit the clinical phenotype of the patients with LPI_{Fin} seems to vary as much as the phenotypes of patients with other SLC7A7 mutations.

In patients with LPI, plasma concentrations of dibasic amino acids are low because of poor intestinal absorption and excessive renal loss [6]. Deficiency of arginine and ornithine restricts the function of the urea cycle and leads to hyperammonemia after dietary loads of protein [1]. The plasma concentrations of alanine, glycine, serine, and citrulline are steadily slightly above the reference values, and the plasma concentrations of glutamine and glutamic acid, believed to reflect nutritional nitrogen load, are often also moderately increased. Mild normochromic anemia with anisocytosis and poikilocytosis is common, and serum ferritin and lactate dehydrogenase concentrations are inappropriately high [8,9].

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Patients with LPI are usually symptom-free when breast-fed, but develop vomiting and diarrhea after weaning and may progress to coma if force-fed with high-protein food. The patients usually develop strong protein aversion in late infancy, fail to thrive, have short stature, and show muscle weakness, osteoporosis, and hepatosplenomegaly. Mental development is normal if episodes of prolonged hyperammonemia have not caused neurological damage. Humoral immune responses are defective in some patients [10], and varicella infections may be exceptionally severe [11]. Some patients develop severe pulmonary and renal complications, of which alveolar proteinosis may be immediately fatal [12,13].

Dietary protein restriction and oral supplementation with citrulline are the cornerstones of treatment of LPI. Citrulline, a urea cycle intermediate and precursor of arginine and ornithine, is a neutral amino acid that is readily absorbed in LPI. Supplementation of protein-containing meals with citrulline improves the function of the urea cycle and allows sufficient protein intake without hyperammonemia. Until recently, the long-term lysine deficiency has been an unsolved problem, as in most patients, even moderate administration of lysine per os causes abdominal cramps and loose stools [14]. Consequently, the patients continuously have lysine deficiency, and the plasma concentrations of other essential amino acids may also be low.

As pregnancy is a significant physiological stress, pregnant patients having inborn errors of metabolism may be at increased risk of developing metabolic decompensation. For example, several cases of hyperammonemia leading to postpartum coma have occurred in women with a urea cycle defect caused by ornithine carbamoyltransferase deficiency [15]. Several manifestations of LPI may potentially cause problems during pregnancy. The functional disorder of urea cycle may lead to periods of hyperammonemia, as in other urea cycle defects. Gestational anemia may be severe, and decreased platelet count may lead to bleeding during or after the delivery. The patients have an increased risk of elevated blood pressure and toxemia, and renal insufficiency may be aggravated during pregnancy. It has also been unclear whether the protein-restricted diet of the mother and the potentially diminished bioavailability of lysine and other essential amino acids for the fetus have short- or long-term adverse effects on child's development. To explore these questions in detail, we now describe the course and outcome of altogether 18 pregnancies of 9 mothers with LPI.

Table 1
Maternal ages, weight gains, and complications during pregnancies and deliveries of the 9 mothers with LPI included in this study and the gestational ages, methods of delivery, birth weights, and Apgar scores of their children

Mother	Delivery	Age at delivery (y)	Weight gain during pregnancy (kg)	Complications during pregnancy	Mode of delivery	Gestational age (wk + d)	Complications during delivery	Sex of the child	Birth weight (g)	Apgar score at 1/5/10 min
1	1	22	13.4	Listerial septicemia	Cesarean	34 + 4		F	2040	9/9
2	1	19	Unknown	Anemia	Emergency cesarean	35 + 5	Placental bleeding after amniotic fluid puncture	M	2480	1/3
	2	29	6.5	Proteinuria	Cesarean	38 + 1	Low hemoglobin (up to 71 g/L)	M	2910	9/9/9
3	1	26	9.1	Toxemia, glucosuria	Cesarean	38 + 0	Low hemoglobin (up to 77 g/L)	F	2600	9/9
	2a	28	7.0	Glucosuria, proteinuria	Cesarean	36 + 5		M	2420	9/9
	2b			(Bigeminal)	Cesarean	36 + 5		F	2190	9/9
	3	35	4.0	Gestational diabetes	Cesarean	39 + 0		M	2620	9/9
4	1	27	Unknown	Toxemia	Cesarean	36 + 1	Acute birth asphyxia of the child	M	2990	1/8/10
	2	32	Unknown	Toxemia	Cesarean	30 + 2	Severe thrombocytopenia, hypertensive crisis	M	1680	7/8
5	1	25	7.0	Toxemia	Cesarean	36 + 0	Pneumothorax of the child	F	2360	9/10
	2	27	9.4	Toxemia	Cesarean	36 + 5	Severe bleeding, hydrocephalus of the child	F	2860	9/10
	3	33	8.2	Toxemia, anemia	Cesarean	37 + 4		F	3010	9/9
6	1	27	8.2	Anemia	Vaginal	38 + 6		F	2710	9/10
7	1	20	13.3	Toxemia	Vaginal	38 + 2	Bleeding	M	3200	8/10
	2	23	6.8	Toxemia	Vaginal	36 + 6	Bleeding, partial retention of the placenta	M	3100	9/9/8
8	1	22	7.3	Anemia	Vaginal	36 + 0		F	3200	8/10
	2	23	Unknown	Anemia	Vaginal	37 + 0		F	3300	9/9
9	1	25	9.8	Proteinuria, anemia	Vaginal	39 + 2	Mild hypoglycemia of the child	F	2900	9/9
	2	29	6.5		Cesarean	34 + 0	Premature labor	F	1820	9/8

2. Patients and methods

2.1. Subjects

Eighteen pregnancies of 9 Finnish mothers with LPI between the years 1978 and 2003 were included in this analysis. All mothers had been diagnosed with LPI between the ages of 0 and 14 years. Their age at the time of delivery varied from 19 to 35 years. Nineteen children were born (8 boys, 11 girls, 1 pair of twins). One of the children was diagnosed after delivery to have LPI. Six of the deliveries were vaginal, 11 were performed by elective cesarean delivery, and 1 by emergency cesarean delivery (Table 1). During pregnancy, the mothers with LPI were seen 5 to 15 times at the local maternity clinics. The blood pressure, body weight, hemoglobin, urinary protein, and glucose were measured on every visit. A more extensive laboratory evaluation was performed at least twice during the pregnancy (Table 2).

Table 2
Laboratory tests taken during pregnancy

Monthly
Urinary orotic acid (morning and evening samples)[a]
Urinary protein measurement[a]
Blood pressure[a]
Bimonthly
Hemoglobin[a]
Hematocrit[a]
Red blood cell count[a]
White blood cell count[a]
Platelet count[a]
Lactate dehydrogenase[b]
Ferritin[b]
Urine analysis[a]
Every 4 mo
Plasma albumin[a]
Prealbumin[a]
Retinol-binding protein
IGF-1
Erythropoietin[a]
Plasma bilirubin
γ-Glutamyltransferase (γ-GT)
Haptoglobin
Thyroxine-binding globulin
Thyrotropin[a]
Free thyroxine[a]
Plasma creatinine[a]
C-reactive protein
Zinc[a]
Copper
Ceruloplasmin
Calcium[a]
Magnesium
Antinuclear antibodies
Immunoglobulins A, G, and M
Plasma amino acids[a]
Urinary amino acids[a]
24-h urinary protein measurement[a]
Creatinine clearance[a]

Samples are serum samples unless otherwise indicated.

[a] The tests should be taken from all the mothers with LPI during pregnancy as represented.

[b] The tests should be taken every 4 months.

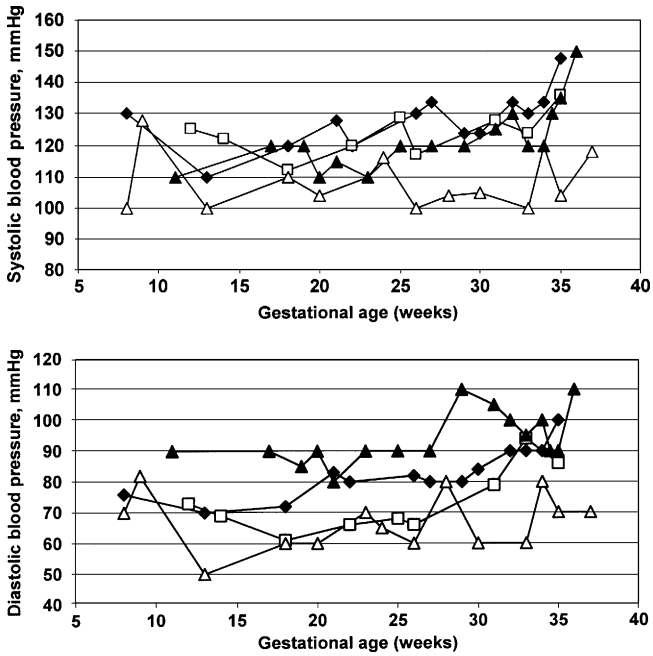

Fig. 1. Systolic and diastolic blood pressure readings during 4 LPI pregnancies, all complicated by toxemia.

2.2. Methods

Concentrations of amino acids in plasma and urine were measured with automatic ion-exchange chromatography (Biochrom 20 Amino Acid Analyzer, Biochrom, Cambridge, UK) with norleucine as an internal standard. The plasma samples were deproteinized with sulfosalicylic acid and then centrifuged. As reference values for plasma amino acids during pregnancy, data from Lopez-Quesada et al [16] were used, whereas for urinary amino acids, reference data from our own laboratory were used. The patients also regularly collected urine samples, which were sent frozen for orotic acid analysis. Urine samples were purified by solid-phase extraction using Bond Elut strong anion-exchange cartridge (Varian, Palo Alto, CA) and analyzed with Agilent 1100 high-performance liquid chromatography system (Agilent Technologies, Palo Alto, CA). Concentrations of insulinlike growth factor 1 (IGF-1) in serum were measured with IGF-1 IRMA 100T Kit (Nichols Institute Diagnostics, San Juan Capistrano, CA). Other analyses were performed using routine laboratory methods.

The Ethics Committee of the hospital approved the study, and informed consent was obtained from the patients for the collection of their records from the maternity clinics and labor wards.

3. Results

3.1. Clinical aspects

The average duration of pregnancy was 36.6 weeks (from 30 weeks 2 days to 39 weeks 2 days). The average gestational age at which the elective cesarean deliveries were performed (n = 12) was 37 weeks. The pregnancies that ended with vaginal delivery lasted 37.7 weeks in average (from 36 weeks to 39 weeks 2 days). One child was delivered by cesarean delivery at 31 weeks because the mother developed a hypertensive crisis. Maternal complications or the elevated risk for them were the main reasons to early induction of labor or to cesarean delivery.

The average weight gain of the mothers during pregnancy was 8.3 kg (range, 4.0-13.4 kg). Mild proteinuria occurred in 3 pregnancies (n = 18), whereas 8 pregnancies were complicated by toxemia (Fig. 1). In 1 patient, toxemia led to a hypertensive crisis. One patient had glucosuria during her first 2 pregnancies and developed gestational diabetes during her third pregnancy. She was not overweight, her weight gain during the pregnancies varied between 4 and 9 kg, and the sizes of the children were appropriate for gestational age.

The size of the placenta varied from 350 to 750 g (mean, 512 g). When adjusted to gestational weeks, maternal pregravid weight, and maternal pregnancy weight gain, 8 of the 16 examined placentas were overweight, suggesting that the children may have had antenatal hypoxia [17]. Fetal-placental ratio varied widely between the patients, and was in 6 pregnancies above (>1 SD, n = 3) or under (< −1 SD, n = 3) the reference range [18].

Complications during delivery were common (Table 1). Three deliveries were complicated by severe bleeding, and 1 child was delivered by cesarean delivery at week 34 because of listerial septicemia of the mother. The mother had symptoms of pneumonia and disseminated intravascular coagulation. The child had no symptoms of an infection, and the ultrasound examination result of her brain was normal at the age of 3 days. The mother was treated with intravenous meropenem and moxifloxacin and recovered well. The child was given a prophylactic course of antibiotics. One child was delivered by emergency cesarean delivery after an ultrasound-guided amniotic fluid puncture that led to placental bleeding. His 1- and 5-minute Apgar scores were 1 and 3, respectively, and he died on the day of the delivery.

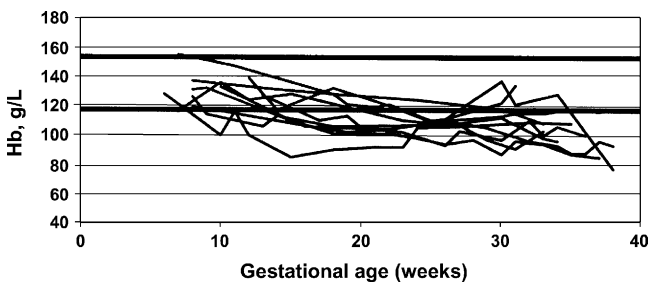

Fig. 2. Blood hemoglobin concentration (reference range, 117-153 g/L, shown by the 2 dark horizontal lines) vs gestational age in mothers with LPI.

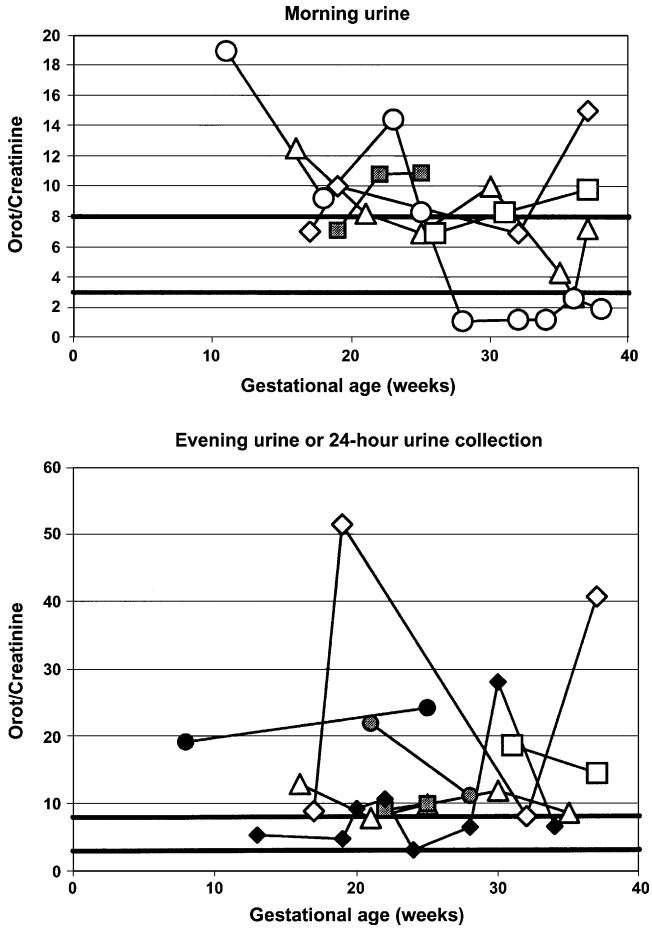

Fig. 3. Orotic acid–creatinine ratio in urine vs gestational age in mothers with LPI. During 2 pregnancies (solid black symbols), 24-hour values were measured instead of morning and evening values.

One girl had moderate hydrocephalus, and a large intracerebral cyst was seen on computed tomography. She developed hemiplegia and needed a shunt operation at the age of 26 days. One child had acute birth asphyxia and needed resuscitation, but recovered well by the age of 10 minutes. Another child had pneumothorax after birth and needed mechanical ventilation for 3 days. One child had mild, transient hypoglycemia. These children have developed normally afterward. Four of the children were small for gestational age (weight < −2 SD of healthy Finnish newborns, Table 1) [19].

3.2. Laboratory findings

Of the 9 mothers, 5 were anemic during at least 1 pregnancy despite routine iron substitution given to all pregnant women (Fig. 2). Two of these mothers received red blood cell transfusions during pregnancy. Thrombocytopenia (platelet count $<150 \times 10^9$/L) developed in 4 of the 9 mothers.

Serum ferritin concentrations, which typically are markedly increased in LPI even in total absence of iron from the bone marrow cells [20], remained almost unchanged during the pregnancy. Serum haptoglobin concentration, measured

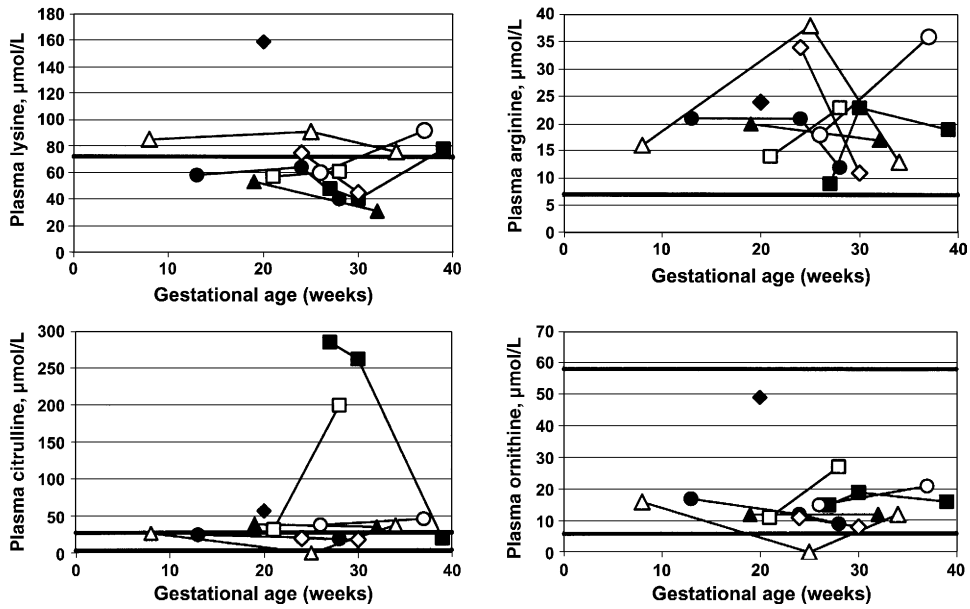

Fig. 4. Concentrations of lysine, arginine, citrulline, and ornithine in plasma vs gestational age in mothers with LPI. Reference values (third-trimester mean ± 2 SD) are 72 to 204, 7 to 71, 4 to 28, and 6 to 58 µmol/L, respectively.

at least twice from 4 patients during 5 pregnancies, was always below the reference range (<0.2 g/L). Serum erythropoietin concentrations were high in all 5 pregnancies in which the values were measured (range, 58-120 U/L; reference range, 12-35 U/L).

Free thyroxin concentration in plasma was decreased during pregnancy in 4 of 5 studied patients. One of these patients had been previously diagnosed with hypothyreosis. Of the remaining 3 patients with low free thyroxin values, 2 had normal concentrations and 1 had decreased concentration of thyrotropin.

Serum retinol-binding protein was within the reference range in 4 of 5 mothers studied, but increased in 1 mother from 63 mg/L at week 20 (reference range, 30-60 mg/L) to 66 mg/L at week 34 and to 126 mg/L 2 weeks after delivery. Of 4 mothers studied, 2 had antinuclear antibodies. Serum IGF-1 concentrations increased as expected [21] during all 5 pregnancies in which IGF-1 values were repeatedly

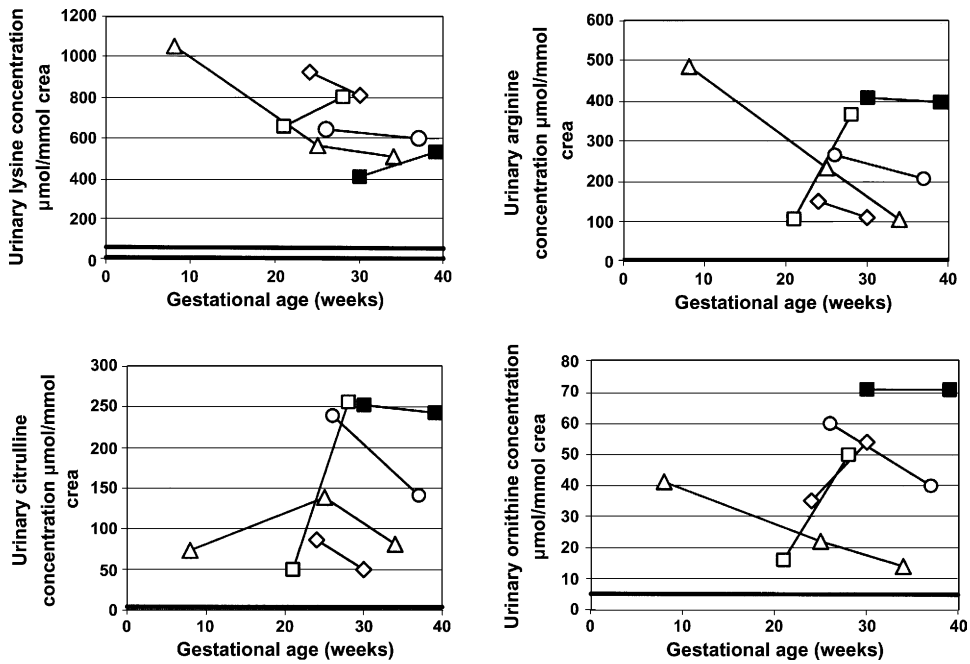

Fig. 5. Concentrations of lysine, arginine, citrulline, and ornithine in urine vs gestational age in mothers with LPI. Reference values are 7 to 58, 0 to 5, 0 to 4, and 0 to 5 µmol/L, respectively.

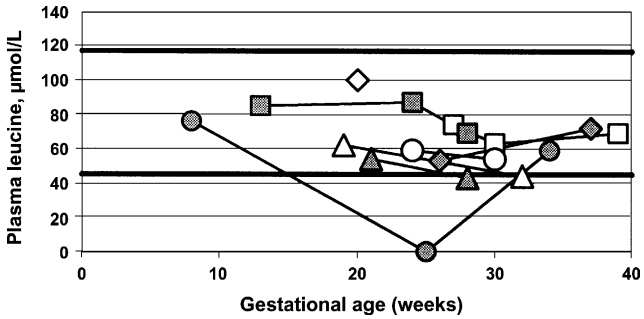

Fig. 6. Plasma leucine concentration vs gestational age in mothers with LPI. Reference values (third-trimester mean ± 2 SD) are 45 to 117 μmol/L.

measured, and all concentrations stayed within the reference range with a few transient exceptions. Serum lactate dehydrogenase activity was characteristically high already before the pregnancy, but decreased slightly during pregnancy, possibly because of hemodilution.

Interestingly, serum calcium concentration decreased in most of the patients instead of increasing, as what happens in normal pregnancies (reference range during pregnancy, 2.25-2.55 mmol/L). This finding is probably in part due to the decreased plasma albumin concentration, as plasma albumin concentrations were constantly at or slightly below the lower reference limit (reference range, 36.1-47.5 g/L during the first trimester and 30-42 g/L during the third trimester; values in mothers with LPI during pregnancy, 24-37.5 g/L). Serum prealbumin concentrations, which in normal pregnancies decrease by 10% to 15%, increased in 3 of the 5 patients studied and were stable in the remaining 2 patients. Of 4 patients studied, 3 had markedly increased serum zinc concentrations (up to 60 μmol/L; reference range, 10-20 μmol/L), and the values increased even further later in 2 of the patients.

Most adult patients with LPI have modest hypertriglyceridemia, and the triglyceride values in all 5 pregnancies, in which the values were measured, were markedly elevated. In 4 of these 5 pregnancies, serum cholesterol values exceeded the recommended value (5 mmol/L). Serum creatinine values stayed within the reference range, except in 1 patient who already had mildly increased creatinine values. Her values remained unchanged during the pregnancy. Serum bilirubin, γ-glutamyltransferase, and magnesium values were within the reference range in all pregnancies in which they were measured. Serum copper, ceruloplasmin, and thyroxine-binding globulin concentrations showed normal increase during pregnancy. Orotic acid–creatinine ratio in spot urine samples varied considerably. As a rule, the ratios were higher in the evening samples than in the morning samples (Fig. 3).

Plasma and urine amino acids were measured repeatedly during 5 pregnancies and plasma amino acids alone during 3 additional pregnancies. In most plasma samples, arginine, glutamine, alanine, and glycine concentrations were normal, but lysine and ornithine concentrations were repeatedly subnormal. Plasma citrulline concentration was within the reference range in 6 of the 8 pregnancies, whereas exceptionally high concentrations were measured during 2 pregnancies (Fig. 4). All the studied patients had increased urinary excretion of lysine, arginine, ornithine, citrulline, alanine, and glycine (Fig. 5). Urinary excretion of glutamine was also increased in 2 patients. Urinary leucine and isoleucine excretion varied markedly. Interestingly, plasma leucine and isoleucine concentrations were constantly decreased (Fig. 6).

4. Discussion

Several features of LPI associate with potential risks to the mother and the fetus during pregnancy and delivery. The most obvious hazard is protein intolerance that carries a risk of postprandial hyperammonemia in case of excessive protein intake, as well as protein deficiency in case of too restricted intake, then causing adverse effects in the mother and the fetus. In the pregnancies we observed, no symptomatic hyperammonemias were detected. Plasma concentrations of glutamine and glutamic acid, alanine, and glycine were within the reference range, indicating adequate function of the urea cycle. However, urinary orotic acid excretion varied considerably, and transient peaks of urinary orotic acid–creatinine ratio may indicate temporary nonoptimal control of nitrogen balance.

In mothers with LPI, protein intake remained low during pregnancy. The mothers gained weight adequately considering their small size, but plasma albumin concentrations were uniformly low, suggesting inadequate protein synthesis. Surprisingly, serum prealbumin concentrations increased during the pregnancy. The subnormal prepregnancy plasma concentrations of lysine and ornithine remained almost unchanged during pregnancy. The fact that plasma concentrations of leucine and isoleucine, 2 essential amino acids, were also low further suggests that the mothers with LPI have deficiency of essential amino acids during pregnancy, probably reflected by the large proportion of infants (21%) that are born small for their gestational age. In animal models, protein restriction during pregnancy reduces nutrient transfer to the fetus and fetal weight [22].

Most patients with LPI have mild anemia, the mechanisms of which are still obscure. Maternal anemia is another significant cause of intrauterine growth retardation [23]. In this study, anemia developed commonly despite proper iron substitution, and red blood cell transfusions were needed in some cases. Serum haptoglobin concentrations were extremely low, indicating active hemolysis. However, serum bilirubin concentrations were never elevated. In patients with LPI, high serum ferritin concentrations are thought to be associated with stress situations [8], but they did not change notably during pregnancy. Platelet counts were subnormal in nearly half of the mothers, and 3 pregnancies were complicated by severe bleeding.

Altogether, 44% of the LPI pregnancies we followed were complicated by toxemia, clearly exceeding the

prevalence of toxemia in normal pregnancies (3%-5% in primigravidas [24]). Maternal risks associated with toxemia are sizeable, including convulsions, cerebral hemorrhage, disseminated intravascular coagulopathy, pulmonary edema, renal failure, liver hemorrhage, and death, and the risks to the fetus comprise intrauterine growth retardation, hypoxemia, acidosis, prematurity, and death [25]. Toxemia indeed seems to be the most prominent complication of LPI pregnancies, possibly explaining several of the maternal and fetal problems encountered. Altered vascular development of the placenta is considered the probable underlying cause for preeclampsia [26]. Unfortunately, no histological examination has been performed on the placentas of mothers with LPI.

Plasma concentrations of several trace elements were measured from the mothers during the pregnancy to detect possible nutritional deficiencies due to the restricted diet. Serum zinc concentrations were unusually high and continued to rise during pregnancy in some patients instead of the normal pregnancy-induced 20% to 30% decrease. Hemolysis of the blood samples drawn is an unlikely explanation for this, as all blood samples were of good quality, and multiple samples were measured from each patient. Only a few cases of real hyperzincemia have been reported [27], and the mechanisms of this condition are largely unknown. Defects in the metabolism of calprotectin, the major calcium- and zinc-binding protein of phagocytes, have been suggested to be associated with this condition [28]. Serum calcium concentration decreased during pregnancy in almost all LPI pregnancies, and 3 of 7 patients had serum calcium concentration below the reference range at the third trimester. In patients with LPI, the concentrations of serum calcium and phosphate are usually within reference ranges, but severe osteoporosis is common, and the patients have a pronounced tendency to have fractures especially in childhood [29]. Although the mothers obviously had poor calcium stores, none of the children developed hypocalcemia.

Thyroxin-binding globulin concentrations showed normal increases [30] in all 5 pregnancies, but in 4 pregnancies, the concentration of free thyroxin was subnormal, suggesting inadequate thyroxin production, potentially limiting child's subsequent neuropsychological performance [31].

In normal pregnancies, renal function improves during pregnancy and plasma creatinine concentration falls significantly [32]. In mothers with LPI, pregnancy did not seem to have much effect to serum creatinine concentrations even in a subject with slightly impaired kidney function already before pregnancy. Interestingly, many of the mothers of this study have progressed to renal insufficiency later in life.

Only one of the mothers in this study did not develop complications during pregnancy, but the child was delivered very prematurely. The children in most of the other pregnancies were delivered before term by induction of labor or by cesarean delivery to avoid maternal complications. In one of our patients, an ultrasound-guided amniotic fluid puncture led to bleeding and perinatal death of the child at 35 gestational weeks, and 1 delivery was complicated by a severe maternal bleeding. The child from this latter pregnancy had an intracerebral cyst, developed hydrocephalus, and has mild hemiplegia at the current age of 21 years. She was also suspected of having slightly delayed mental development, but she later successfully attended a normal school. She has gone through several shunt revisions and had a cerebral infarction at the age of 19 years but has made a good recovery. The other children had no anomalies or birth injuries, and their later development has been normal.

Several mechanisms, including poor maternal protein nutrition, maternal anemia, and toxemia, increase the risks of intrauterine growth retardation in LPI. Children that are small for their gestational age may be exposed to a number of health problems later in life, such as elevated blood pressure [33] and abnormal function of the endocrine pancreas [34]. In epidemiological studies, exposure to famine during gestation has been associated with impaired glucose tolerance in adulthood [35]. According to the Barker [36] hypothesis, adaptation of the fetus to a limited supply of nutrients permanently changes its physiology and metabolism in a way that may later lead to several serious illnesses.

Clearly, the patients with LPI carry increased risk for complications during pregnancy and delivery. However, confirming the findings in some previous case histories [6,37], several pregnancies and deliveries were completed successfully. Despite the maternal complications, the children also have a rather good prognosis.

We suggest that the follow-up protocol presented in Table 2 might be of value for monitoring of the pregnancies of the mothers with LPI. For the detection of the development of toxemia early, blood pressure and urinary protein should be measured at least once a month, and complete urinary analysis should be made at least every second month. Nitrogen overload should also be excluded by monthly measurement of urinary orotic acid. Blood count should be examined bimonthly because of the risk for anemia and bleeding. Serum erythropoietin should be measured at least once during the pregnancy. Plasma albumin and prealbumin, plasma and urinary amino acids, and serum calcium should be measured once in 4 months to detect the possible nutritional deficiencies. Serum zinc should also be monitored because some patients in this study develop marked hyperzincemia, the mechanism and significance of which remain unknown. Serum lactate dehydrogenase and serum ferritin levels did not change noticeably during any of the pregnancies, suggesting that the value of those measurements is probably minimal. As the mothers also have elevated risk for hypothyroidism and renal insufficiency, the concentrations of thyrotropin, free thyroxine, and serum creatinine together with creatinine clearance should also be measured once or a few times during the pregnancy.

In summary, our data show that the women with LPI are at markedly increased risk for toxemia and several other complications during pregnancy. Careful follow-up of blood

pressure and some laboratory parameters are essential, and follow-up of the pregnancies and the deliveries should be centralized to experienced units with capability to deal with the common complications. The children of the mothers with LPI generally do well and develop normally, assuming that serious complications during pregnancy and delivery have been avoided. However, intrauterine growth retardation is common, suggesting that these children may be particularly prone to develop some multifactorial diseases much later in life.

Acknowlegment

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