Human Placental Lactogen: A Predictor of Perinatal Outcome?

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Serial human placental lactogen (hPL) determinations were performed on 806 women with normal and abnormal pregnancies late in the pregnancy. These results were not reported to the clinicians involved. For the study population as a whole, low hPL levels did not effectively predict those adverse perinatal outcome variables evaluated. Further analysis revealed that this was true both for the normal and abnormal pregnancy groups. Our data do not support the routine use of antepartum hPL screening, as advocated by others, as a means of improving perinatal outcome. In certain at-risk patients, there was an association between low hPL values and the presence of 1 or more of the adverse outcome variables. However, these patients had been recognized clinically as having fetuses in jeopardy.

The clinical utility of serum human placental lactogen (hPL) determinations in improving perinatal outcome has not been clearly defined. Certain reports suggest that this test may be of value in monitoring abnormal pregnancies,[1,2] while others are less hopeful in this regard.[3,4] Low hPL levels have been reported by some to correlate with adverse fetal/neonatal outcome in clinically normal pregnancies as well[5,6]; others have not found the test to be helpful in the clinically normal patient.[4,7]

A clinical study was undertaken at the University of Iowa College of Medicine to determine whether hPL determinations are beneficial. The questions asked were: 1) Would routine antepartum hPL testing improve perinatal results? 2) In clinically normal pregnancies would low hPL values effectively predict adverse perinatal outcome? and 3) In clinically abnormal pregnancies would hPL testing provide information regarding perinatal outcome additional to that provided by current clinical and laboratory fetal surveillance?

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Materials and Methods

Volunteers from the high-risk and routine antepartum clinics were enrolled in the study from September 1976 through June 1977. The only entry requirements were the presence of a living fetus and the absence of labor. At each antepartum visit from 34 weeks' gestation until delivery, a serum sample was obtained which was analyzed in duplicate for hPL by radioimmunoassay using a standard commercial kit (New England Nuclear). Hospitalized patients had samples obtained weekly.

So that obstetric management would not be influenced by the serum hPL levels, hPL results were not reported.

Following delivery, data sheets were completed using information from the hospital records of the mothers and newborns. Demographic data, identified risk factors, fetal surveillance test results, neonatal outcome data, and hPL values were recorded and subsequently transferred to magnetic tape for computer analysis.

Eight hundred six patients with at least 1 hPL determination delivered at University Hospitals. They and their 818 offspring (12 sets of twins) form the study population.

Patients were categorized as follows. Groups 1 and 2 consisted of patients whose pregnancies were defined as being at risk prior to labor because 1 or more of the following events had occurred: antepartum admission to the hospital, antepartum fetal heart rate (FHR) testing, urinary estrogen determination, or amniocentesis for fetal maturity testing and/or Δ OD (optical density) 450 nm determination. Risk patients were placed in group 1 if they spontaneously went into labor (despite their risk status, the clinical opinion apparently was that induction of labor was not required in these patients). Risk patients were assigned to group 2 if delivery was effected because of concern for the mother and/or fetus. In these patients induction of labor was carried out or cesarean sections were performed before labor had begun. Patients in group 3 were not considered to be at risk prior to labor. They were not

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admitted to the hospital prior to labor, nor did they undergo antepartum FHR testing, urinary estrogen assays, or third-trimester amniocenteses. Some of these group 3 patients may have been high risk because of maternal age, socioeconomic status, or other factors, but the specific clinical and laboratory measures generally undertaken in pregnancies we consider to be at risk were absent. It should be emphasized that these operational definitions of groups 1–3 were established at the beginning of the study, and the assignment of a particular patient to a particular group was independent of her serum hPL levels or the perinatal outcome.

Adverse outcome variables of interest were perinatal death, intrauterine growth retardation (IUGR), congenital anomalies, meconium-stained amniotic fluid, FHR abnormalities in labor, fetal acidosis (pH < 7.25) in labor, 5-minute Apgar score < 8, and the need for immediate neonatal resuscitation. Although the significance of meconium-stained amniotic fluid remains controversial, it was selected as an adverse outcome variable because it has been included as such in previous hPL studies.[5,6]

If there was a discrepancy between the clinical estimate of gestational length and that suggested by physical examination of the newborn, the latter was chosen as indicating gestational age. Appropriateness of birth weight for gestational age was determined from the Colorado growth chart.[8]

Low hPLs were defined as those values within the approximate $2\frac{1}{2}$ percentile for each week of gestation (34–43 weeks) in 404 normal pregnancies. These 404 patients were in group 3 (not at risk) and delivered living singleton fetuses weighing from 2500 to 4000 g who had 5-minute Apgar scores ≥8 and who required no resuscitation. A patient was placed in the low hPL category if any single value was low.

The study patients were categorized as having normal or low hPL levels. The outcome variables were compared for patients having normal or low hPL measurements for the study population as a whole, individually for groups 1–3, and for separate risk factors in groups 1 and 2. Fisher's exact test was employed to determine the statistical significance of the differences observed.

Results

This study focuses on perinatal outcome. Details of the study population and certain physiologic and pathophysiologic hPL relationships are the subjects of a separate report.[9]

Seven hundred seventy-two babies (94%) were delivered of mothers with normal serum hPL values; 46 babies (6%) were delivered of mothers with low serum hPL values. Table 1 compares the low and normal hPL groups in terms of the presence or absence of the specific adverse outcome variables. The figures in parentheses represent percentages within each column for each variable.

Perinatal Deaths

None of the 9 perinatal deaths occurred in patients with low hPL levels. There were 4 fetal deaths (2 of unknown cause in clinically normal patients; 1 fetus in a twin pregnancy; 1 growth-retarded fetus in a patient with hypertension). Five babies died neonatally (1 following severe asphyxia secondary to premature separation of the placenta; 1 set of twins because of presumed coxsackievirus infection; 2 secondary to cardiac anomalies).

IUGR

In the low-hPL group, 7% were growth retarded, versus 2% in the normal-hPL group (Table 1). The apparently increased tendency for the low-hPL group to be associated with growth-retarded babies is not statistically significant. Furthermore, 93% of the babies delivered of women with low hPL values were not growth-retarded, and the low-hPL group accounted for only 17% of the growth-retarded babies in the study.

Congenital Anomalies

There was no difference between the low- and normal-hPL groups in this category.

Meconium Staining of the Amniotic Fluid

Again, no difference was noted. Only 6% of the babies with meconium-stained amniotic fluid were in the low-hPL group.

Abnormal FHR

Fetal heart rate abnormalities in labor were recorded in 141 cases. There was no significant difference in distribution between the low- and normal-hPL groups. The low-hPL group accounted for 7% of the fetuses with FHR abnormalities.

Fetal Acidosis

Scalp blood pH determinations were performed on 93 fetuses. None of the 17 acidotic fetuses (pH < 7.25) were in the low-hPL group.

Low 5-Minute Apgar Scores

Infants with low 5-minute Apgar scores (<8) occurred with equal frequency (7%) in the low- and normal-hPL

Table 1. Correlation of Adverse Perinatal Outcome Variables with hPL Values for Entire Study Population

Variable	hPL					
	Low		Normal		Total	
Perinatal death	0	(0)	9	(1)	9	(1)
No perinatal death	46	(100)	763	(99)	809	(99)
Total	46	(100)	772	(100)	818	(100)
IUGR	3	(7)	15	(2)	18	(2)
No IUGR	43	(93)	757	(98)	800	(98)
Total	46	(100)	772	(100)	818	(100)
Anomaly	1	(2)	16	(2)	17	(2)
No anomaly	45	(98)	756	(98)	801	(98)
Total	46	(100)	772	(100)	818	(100)
Meconium noted	8	(17)	117	(15)	125	(15)
Meconium not noted	38	(83)	665	(85)	693	(85)
Total	46	(100)	772	(100)	818	(100)
Abnormal FHR	10	(22)	131	(17)	141	(17)
FHR normal	36	(78)	641	(83)	677	(83)
Total	46	(100)	772	(100)	818	(100)
pH low (< 7.25)	0	(0)	17	(20)	17	(18)
pH normal (≥ 7.25)	8	(100)	68	(80)	76	(82)
Total	8	(100)	85	(100)	93*	(100)
5-minute Apgar score < 8	3	(7)	51	(7)	54	(7)
5-minute Apgar score ≥ 8	43	(93)	721	(93)	764	(93)
Total	46	(100)	772	(100)	818	(100)
Resuscitation needed	8	(17)	158	(20)	166	(20)
Ressuscitation not needed	38	(83)	614	(80)	652	(80)
Total	46	(100)	772	(100)	818	(100)
Vascular resuscitation needed	1	(2)	24	(3)	25	(3)
Vascular resuscitation not needed	45	(98)	748	(97)	793	(97)
Total	46	(100)	772	(100)	818	(100)

$P > 0.10$ for all variables.
Figures in parentheses are column percentages for each variable.
hPL = Human placental lactogen; IUGR = intrauterine growth retardation; FHR = fetal heart rate.
* Ninety-three fetuses had fetal blood sampling.

groups. Because 1-minute Apgar scores were not entered on our data sheets and because with early effective resuscitation a depressed baby at birth might have a high 5-minute score, the need for and type of neonatal resuscitation were also evaluated.

Need for Neonatal Resuscitation

Only 5% of the 166 babies requiring resuscitation were in the low-hPL group.

Need for Vascular Resuscitation

Twenty-five babies were depressed enough at birth to require vascular resuscitation (sodium bicarbonate and/or plasma protein) in addition to oxygen. The frequency of infants in the low- and normal-hPL groups did not differ.

For the study population as a whole, assignment to the low-hPL group was without predictive value concerning the adverse outcome variables that were studied. The frequency of adverse outcome was the same in the low- and normal-hPL groups; a large majority in the low-hPL group was without each of the adverse outcome variables evaluated.

Separate evaluation of groups 1–3 gave similar negative results. Group 3 (not at risk antepartum) consisted of 576 babies. Twenty-eight (5%) infants were delivered of mothers with low hPL levels. The low-hPL group had either no association or a lower frequency of association, with 5 of the adverse outcome variables (perinatal death, congenital anomalies, fetal acidosis, the need for resuscitation, and the need for vascular resuscitation) compared with the normal-hPL group (N = 518). Data for the other 4 variables are

Table 2. Correlation of Adverse Perinatal Outcome Variables with hPL Values in Group 3*

Variable	hPL					
	Low		Normal		Total	
IUGR	1	(4)	8	(1)	9	(2)
No IUGR	27	(96)	540	(99)	567	(98)
Total	28	(100)	548	(100)	576	(100)
Meconium noted	6	(21)	90	(16)	96	(17)
Meconium not noted	22	(79)	458	(84)	480	(83)
Total	28	(100)	548	(100)	576	(100)
Abnormal FHR	5	(18)	74	(14)	79	(14)
FHR normal	23	(82)	474	(87)	497	(86)
Total	28	(100)	548	(100)	576	(100)
5-minute Apgar score < 8	3	(11)	32	(6)	35	(6)
5-minute Apgar score ≥ 8	25	(89)	516	(94)	541	(94)
Total	28	(100)	548	(100)	576	(100)

$P > 0.10$ for all variables.
Figures in parentheses are column percentages for each variable.
hPL = Human placental lactogen; IUGR = intrauterine growth retardation; FHR = fetal heart rate.
* Group 3 = Patients not considered to be at risk prior to labor.

shown in Table 2. Again, no statistically significant differences were observed between the low- and normal-hPL groups.

Two hundred forty-two babies were delivered of mothers in the at-risk groups 1 and 2. Mothers were assigned to the risk groups based on medical (eg, diabetes mellitus and chronic hypertension) and obstetric [eg, premature rupture of the membranes (PROM) without labor, third-trimester bleeding, and preeclampsia] factors.

One hundred forty-four babies were delivered of mothers in group 1. Although increased risk explained certain management steps (eg, antepartum FHR testing) not taken in group 3 patients, no indicated effecting of delivery was undertaken. Ten of these babies (7%) were delivered of mothers with low hPL levels. This low-hPL group had no association or a lower frequency of association with 8 of the 9 adverse outcome variables than did the normal-hPL group ($N = 134$). Data for the remaining variable (meconium-stained amniotic fluid) showed no real differences (Table 3).

There were 98 babies delivered to mothers in group 2. These at-risk patients had delivery effected by indicated induction of labor or by cesarean section performed before labor had begun. Eight of these babies (8%) were delivered of mothers with low hPL levels. This low-hPL group had no association or a lower frequency of association with 4 of the 9 adverse outcome variables (perinatal death, meconium-stained amniotic fluid, fetal acidosis, and low 5-minute Apgar score) than did the normal-hPL group ($N = 90$). The 5 remaining variables are considered in Table 4. In group 2 patients with low hPL levels there is a suggestion of an increased rate of IUGR (statistically significant) and FHR abnormalities (not statistically significant) when compared with group 2 patients with normal hPL levels, although the small numbers limit interpretation. The 11 low-hPL adverse variable entries in Table 4 represent 6 patients (3 with hypertension, 1 with renal disease and suspected IUGR, and 2 with PROM without labor). Five of the 6 patients had had amniotic fluid maturity testing and/or antepartum fetal well-

Table 3. Meconium-Stained Amniotic Fluid as Related to hPL Values (Group 1)

	hPL					
	Low		Normal		Total	
Meconium noted	2	(20)	21	(16)	23	(16)
Meconium not noted	8	(80)	113	(84)	121	(84)
Total	10	(100)	134	(100)	144	(100)

$P = 0.80$.
Figures in parentheses are column percentages.
hPL = Human placental lactogen.

being testing. All 6 patients were admitted to the hospital prior to labor and had indicated inductions of labor. Their doctors made their management decisions without knowledge of the low-hPL test results.

Analysis of outcome by specific risk factors for the low- and normal-hPL groups did not demonstrate hPL testing to be of predictive value.

Discussion

In a recent review, Spellacy summarized the literature regarding control factors for hPL and clinical studies of hPL as a placental function test.[10] It had been noted previously that hypertensive women who sustained intrauterine fetal deaths tended to have low hPL levels, and it was suggested that serum hPL might serve as a test of placental function.[11] A prospective study of a high-risk clinic population (both hypertensive and normotensive) resulted in fewer perinatal deaths if low hPL results were reported than if they were not.[1] Ylikorkala found that low hPL levels were associated with fetal distress and/or IUGR in a variety of pregnancy complications.[2]

Following these earlier observations, the potential usefulness of hPL testing as an adjunct in obstetric management was extended from use in hypertensive patients to use in general high-risk patients, and finally, with the studies of Letchworth and Chard[5] and England et al,[6] to use as a general screening test in normal pregnancies.

Other workers have been less enthusiastic. They have found the test to be less helpful in predicting perinatal outcome or altering clinical management in high-risk or normal patients.[3,4]

In a separate report based on these 806 women with normal and abnormal pregnancies, we have demonstrated a significant correlation between hPL levels and birth weight and have noted mean hPL differences in conditions where large or small placentas are anticipated.[9] In the present report, however, we are unable to demonstrate a relationship between low hPL values and adverse perinatal outcome. Why?

Placental weights are correlated in a positive manner with serum hPL levels. The placenta in patients with hypertension or with growth-retarded fetuses tends to be small. Patients with these conditions are predisposed to adverse perinatal outcome. Therefore, it is not surprising that some patients with these entities and low hPL levels have problems. This association does not, however, establish that serum hPL can serve as a clinically useful marker of placental function or as an effective predictor of perinatal outcome. The production of this hormone is related to placental size, but considerable variation exists. Although the mean hPL level of patients with growth-retarded fetuses is significantly lower than that of patients whose

Table 4. Correlation of Adverse Perinatal Outcome Variables with hPL Values (Group 2)

Variable	hPL				Total	
	Low		Normal			
IUGR	2	(25)	1	(1)	3	(3)
No IUGR	6	(75)	89	(99)	95	(97)
Total	8	(100)	90	(100)	98	(100)
$P < 0.05$						
Anomaly	1	(13)	0	(0)	1	(1)
No anomaly	7	(88)	90	(100)	97	(99)
Total	8	(100)	90	(100)	98	(100)
$P = 0.08$						
Abnormal FHR	5	(63)	30	(33)	35	(36)
FHR normal	3	(38)	60	(67)	63	(64)
Total	8	(100)	90	(100)	98	(100)
$P = 0.10$						
Resuscitation needed	2	(25)	17	(19)	19	(19)
Resuscitation not needed	6	(75)	73	(81)	79	(81)
Total	8	(100)	90	(100)	98	(100)
$P = 0.82$						
Vascular resuscitation needed	1	(13)	3	(3)	4	(4)
Vascular resuscitation not needed	7	(88)	87	(97)	94	(96)
Total	8	(100)	90	(100)	98	(100)
$P = 0.97$						

Figures in parentheses are column percentages for each variable.
hPL = Human placental lactogen; IUGR = intrauterine growth retardation; FHR = fetal heart rate.

fetuses are not growth retarded,[9] the overlap between the 2 groups limits the predictive value of the test. Ninety-three percent of our patients with low hPL levels gave birth to babies who were not growth retarded. Furthermore, the important transport functions of the placenta may be independent of the placenta's ability to produce hPL. Blood levels of another placental hormone, progesterone, have not been helpful in clinical obstetric management.[12]

It should be emphasized that those group 2 patients in this study with low hPL levels and an apparently increased frequency of certain adverse outcome variables had been identified clinically without knowledge of the hPL test results. Therefore, in the one subset of the study population where there may be a relationship between low hPL levels and adverse outcome (group 2), the test apparently would not have provided *additional* information. The decision to deliver these patients had already been made.

In the hands of the authors routine hPL screening would result in many false positives, ie, low hPL levels in patients who did not have adverse perinatal outcome. The increased concern for patients with low hPL levels might result in additional expense in fetal surveillance and possibly in iatrogenic prematurity as well. In this study, low hPL levels were defined as those within the approximate $2\frac{1}{2}$ percentile of carefully characterized normal patients. This is consistent with levels chosen by other authors of large series.[2,13] Although a less rigidly selected low-hPL group would include more patients with adverse perinatal outcome, the problem with false positives would likewise be expected to be greater.

Possible explanations for our failure to find low hPL levels to be of predictive value may relate to differences in our patient population or in our clinical management. For example, patients with preeclampsia who do not respond rapidly to in-hospital treatment on our service are generally delivered.

This study was designed to evaluate the clinical utility of hPL determinations in late pregnancy. Our data do not support the use of hPL testing as a routine screening procedure to improve perinatal outcome. Low hPL values did not effectively predict adverse perinatal outcome in clinically normal patients. In clinically abnormal pregnancies our tentative conclusion is that hPL determinations did not provide information regarding perinatal outcome over and above that provided by our current clinical and laboratory fetal surveillance. A definite statement cannot be made, however, because the numbers of patients in specific risk categories (eg, chronic hypertension) are not large enough to permit meaningful evaluation. Others are encouraged to study hPL testing in their high-risk patient populations on a blind or prospectively controlled basis. The value of the test, if any exists, must be in providing additional information to that obtained by the careful clinician using the currently available diagnostic tools.

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