INCIDENCE OF NEONATAL HYPOGLYCEMIA

by

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ABSTRACT

40 well neonates had blood glucose determinations made at birth, 3-4 hours after birth, 12-18 hours after birth and after 48 hours after birth. Maternal blood glucose was sampled by fingerstick within one half hour of delivery. All blood glucose determinations were made using Dextrostix and the Ames Reflectance Meter.

A general pattern of mean blood glucose level changes for these samples was found. Some interesting variations were identified in relation to sex, time of first feeding and length of labor. A 10 per cent incidence of hypoglycemia was found.

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INCIDENCE OF NEONATAL HYPOGLYCEMIA

Hypoglycemia in the infant of a diabetic mother has been recognized and its mechanism fairly well understood[1] for many years. Transient neonatal hypoglycemia, in infants of non-diabetic mothers, is not well understood. It is reported to be associated with small size for gestational age,[2-6] birth asphyxia and/or respiratory distress syndrome,[3,5,6] low birth weight in male infants,[7] toxemia in the mother,[2,5,7] and smaller size in a twin birth.[2,5,7] Other associated conditions which have been identified are prematurity,[5,6] cold stress or hypothermia,[5,6] erythroblastosis,[5,6] and polycythemia.[7]

A number of factors have been identified which may operate singly or in combination to produce transient neonatal hypoglycemia. Decreased glycogen storage due to prematurity (with less time to build up stores) or intrauterine growth retardation (resulting in fewer liver cells in which to store glycogen)[8] leads to an infant with deficient reserves of glycogen to meet stress needs. The decreased liver function, particularly gluconeogenesis, of the newborn is exacerbated by prematurity,[1] increasing the difficulty of having available glucose to meet metabolic needs. Glycogen stores may be depleted by conditions such as anoxia in utero, birth asphyxia, cold stress, or hypermetabolism (due to increased number of cells per unit of body weight as in intrauterine growth retardation).[3,6,9,10] If there is a mandatory period of fasting following birth, the infant who has minimal stores or has used most of his stores has no readily available reserve of glucose to meet physiological needs. This may become apparent as hypoglycemia. It is likely that there are other as yet unidentified factors which also contribute to the development of transient neonatal hypoglycemia.

Incidence of neonatal hypoglycemia in studies reported in the literature varies from 0.13%[5] to 67%[3] with numerous values between these figures.[2,11-15] It is difficult to discuss this variation in incidence due to the variance of infant populations studied, the differing level of blood glucose used to define hypoglycemia (from 20 to 40 mg/100 ml.), differing laboratory methods used to measure glucose level, and unknown relationship of testing time to feeding times in most instances. Some studies have related incidence and symptoms; however, the literature includes such a wide range of symptoms that it appears to encompass nearly any newborn behaviour.[4,5,16] Most symptoms reported could also be symptoms of other metabolic imbalances, sepsis, heart disease, brain damage, chromosomal abnormalities, drugs in the mother's circulation, overheating,[17] perinatal anoxia, intracranial hemorrhage, or meningitis.[12]

Many studies report a relationship of neonatal hypoglycemia leading to central nervous system damage.[3,8,18,19] Others dispute this[20] or question whether the hypoglycemia results from central nervous system damage. Some long-term studies following infants with known hypoglycemia show clear evidence of neurological damage[10,19,21] while others demonstrate no significant damage.[20]

In view of the lack of clear evidence regarding the incidence of transient neonatal hypoglycemia in normal infants, the effect of feeding times on the incidence or the relationship of hypoglycemia to symptomatology, it seems important to evaluate these factors.

Research questions posed in this study were: What is the incidence of hypoglycemia in a well newborn nursery? How does a mandatory fasting period affect the incidence of hypoglycemia? Is there any relationship between hypoglycemia and symptoms and other factors reported as associated with hypoglycemia?

SUBJECTS AND METHODS

The sample included all normal infants born at a general hospital during a four week period having parental consent for inclusion in the study. Infants of diabetic mothers, infants who were ill, and/or infants born by Caesarean section were excluded from this study.

The blood glucose level of all infants was determined using Dextrostix with the Ames reflectance meter. Dextrostix are plastic strips impregnated with a highly purified glucose oxidase, peroxidase and chromagen indicator system.[22] The Ames reflectance meter is a battery operated portable meter which "measures the reflected light from the surface of the strip and electronically converts the light energy to an electrical signal which is read out on a meter scale."[22]

The reflectance meter/Dextrostix system has been evaluated in a number of studies and correlates well with blood glucose values obtained by other methods.[22-28]

At birth, cord blood was obtained for determination of blood glucose. Maternal blood glucose was determined within one-half hour of delivery using capillary blood from a fingerstick. Shortly after birth a physical assessment of the infant was made. Gestational age was estimated using Dubowitz' criteria.[29] An estimate of size for gestational age was made using Battaglia and Lubchenco's classification scheme.[30] Gestational history was obtained and recorded. Glucose determinations were made on infant capillary blood obtained by a heelstick in a warmed heel at 3-4 hours of age (before any feedings), repeated between 12 to 18 hours of age and again after 48 hours of age.

Data were examined using the Univac 1108 Computer to compute Pearson r correlations, point-biserial correlations,[31] and correlated t-tests. Uncorrelated t-tests were computed using the Olivetti Underwood Programma 101. Statistical significance was determined using Snedecor and Cochran's tables for a two-tailed t-test.[32] (Correlations and t-tests achieving statistical significance are indicated on the graphs and in the results.)

RESULTS

Figures 1-8 graphically present mean blood glucose levels ± 1 S. D. for all sampling times in all infants and in infants divided into various categories.

<u>All infants</u>. As can be seen in Figure 1, there is a drop in mean blood glucose levels from birth to 3-4 hours, then a reversal of the direction of change with continual small rises until the final reading. The final mean level after 48 hours has not returned to the birth mean level.

<u>Sex differences</u>. (Figure 2). Male mean blood glucose levels are initially higher than female levels, drop slightly lower by 3-4 hours and remain lower than mean female levels in subsequent samples. The standard deviation of male blood glucose levels at birth is much greater than that of females. However, there is a significant difference between male and female mean levels at birth ($p<.05$).

<u>Time of initial caloric ingestion</u>. (Figure 3). Infants fed a source of glucose before 12 hours of age have a lower mean blood glucose level at the 3-4 hour sample than those infants fed a source of glucose after 12 hours. The mean blood glucose level of those fed after 12 hours continues to fall until the 12-18 hour sample. After 48 hours there is little difference in mean blood glucose levels of both groups.

Although hospital routine provided that infants will be NPO for 6 to 12 hours after birth and then fed only sterile water for three feedings before beginning formula, in practice, the time of feeding was variable.

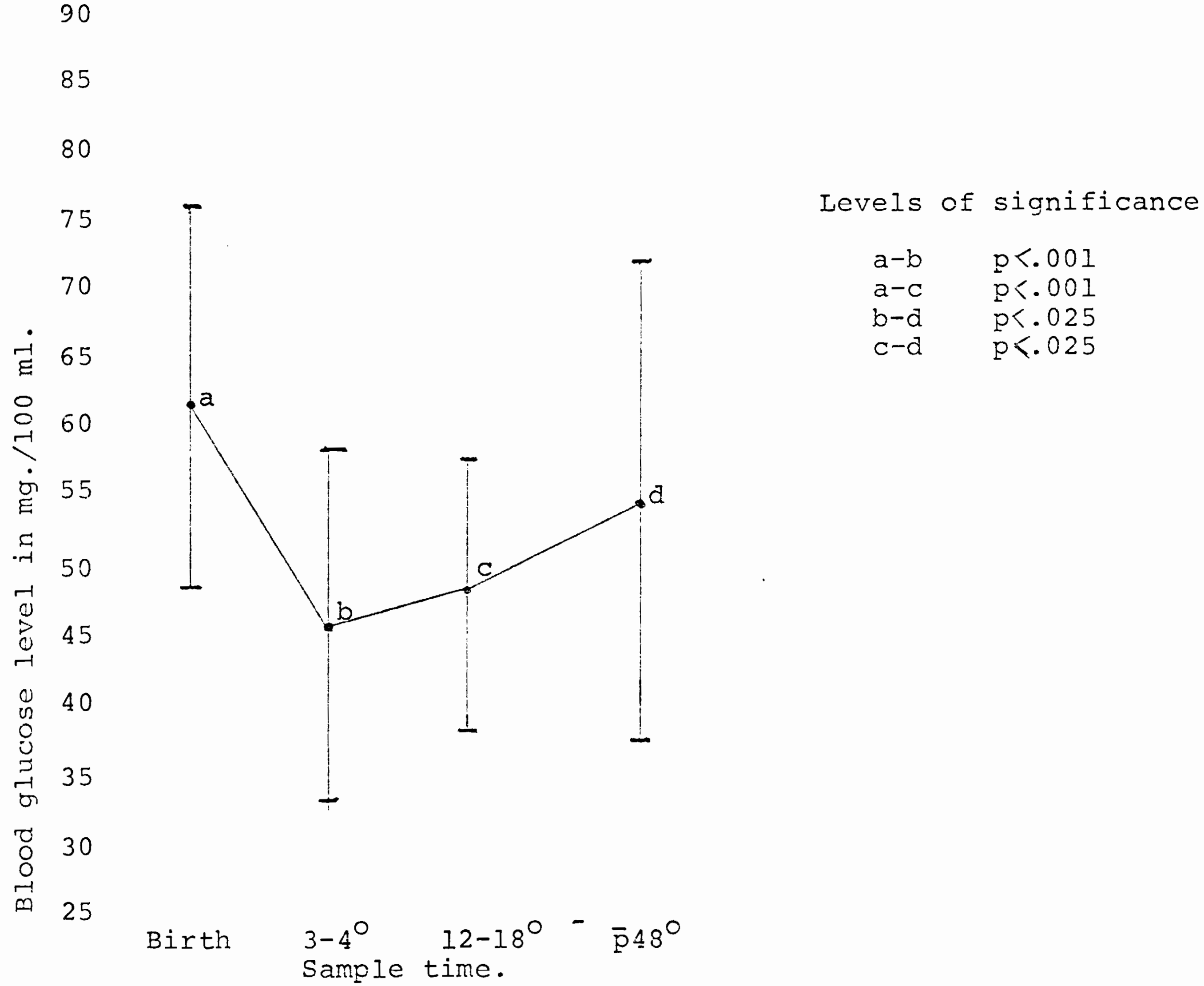

Figure 1. Mean blood glucose levels ±1S.D. for all infants in relation to time after birth (N=39).

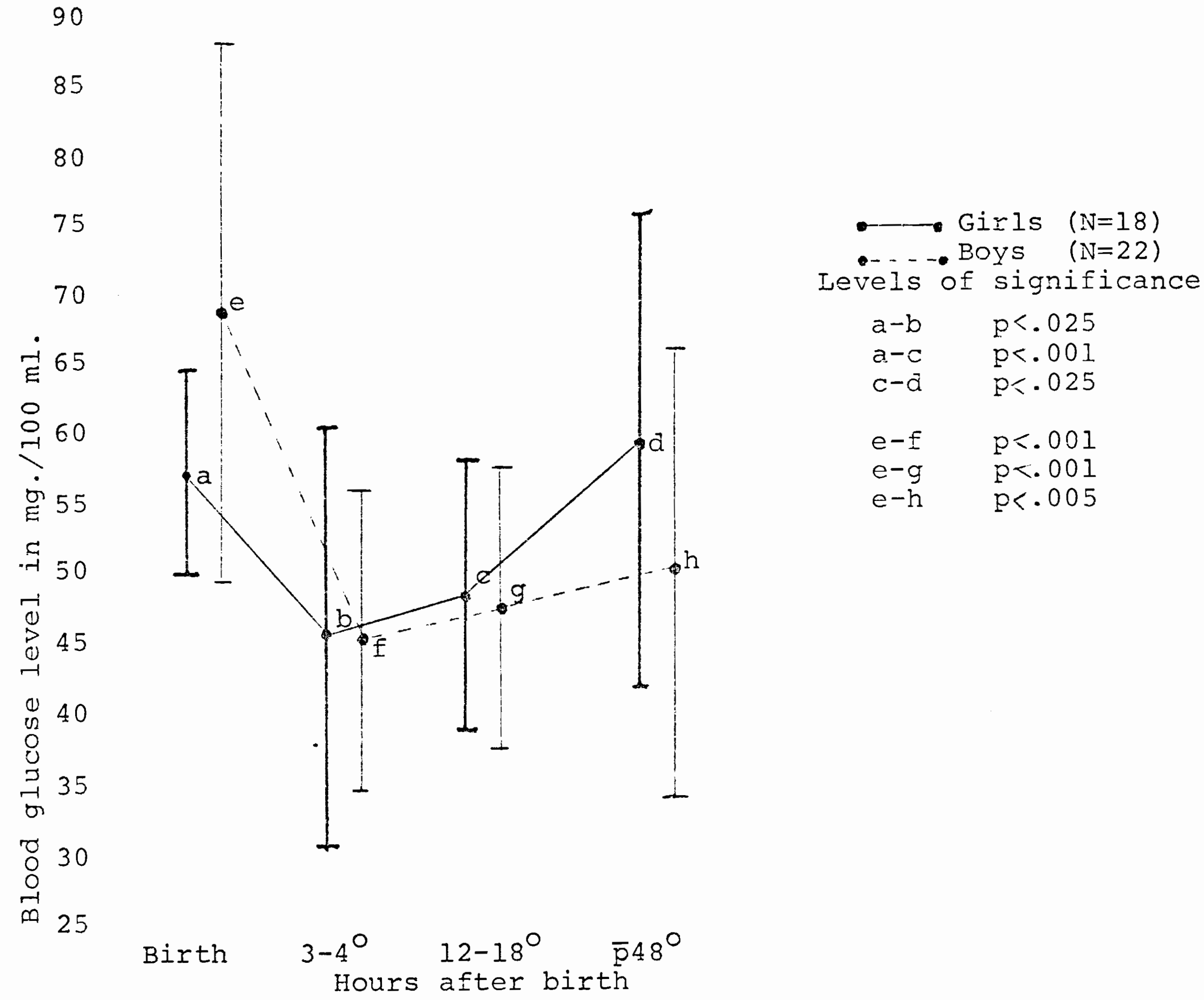

Figure 2. Mean blood glucose levels ±1S.D. for girls and boys in relation to time after birth.

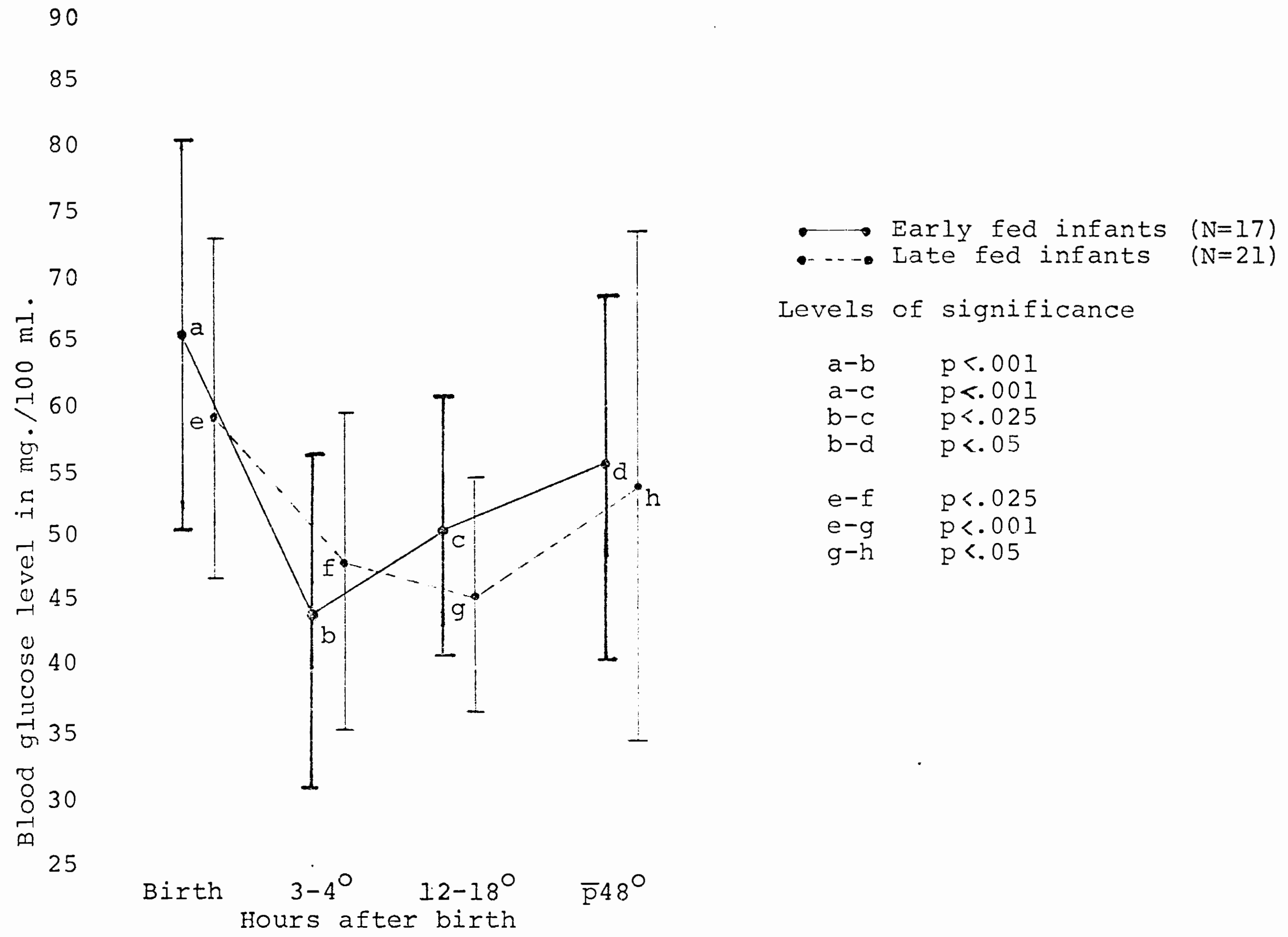

Figure 3. Mean blood glucose levels $\pm$1S.D. for early fed infants (fed before 12°) and late fed infants (fed after 12°) in relation to time after birth.

TABLE I RANGE OF INITIAL CARBOHYDRATE FEEDING TIMES

Type of initial carbohydrate feeding	Earliest age of feeding	Latest age of feeding
Breast	5 hours, 14 minutes	20 hours, 35 minutes
Glucose water or formula	4 hours, 42 minutes	22 hours, 25 minutes

Type of feeding. (Figure 4). There were no significant differences between the mean blood glucose levels for bottlefed or breastfed infants at any sample time. In samples after birth, bottlefed infants had slightly lower mean blood glucose levels.

Length of labor. (Figure 5). (The mean length of labor in this study was 6 hours and 23 minutes. For the purpose of this study labors under 7 hours were clasified as shorter labors, labors over 7 hours were classified as longer labors.) Infants born following longer labors had a slightly higher initial mean blood glucose level which fell by the 3-4 hour sample, then rose slightly, falling again by the time of the sample taken after 48 hours. The difference between the means of the samples taken after 48 hours is not statistically significant.

Symptoms. (Figure 6). Presence or absence of symptoms (apathy, cyanosis, high-pitched or weak cry, hyperactivity, jitteriness and/or tremors) had no sifnificant effect on mean blood glucose levels. The large standard deviation of the symptomatic group is apparent.

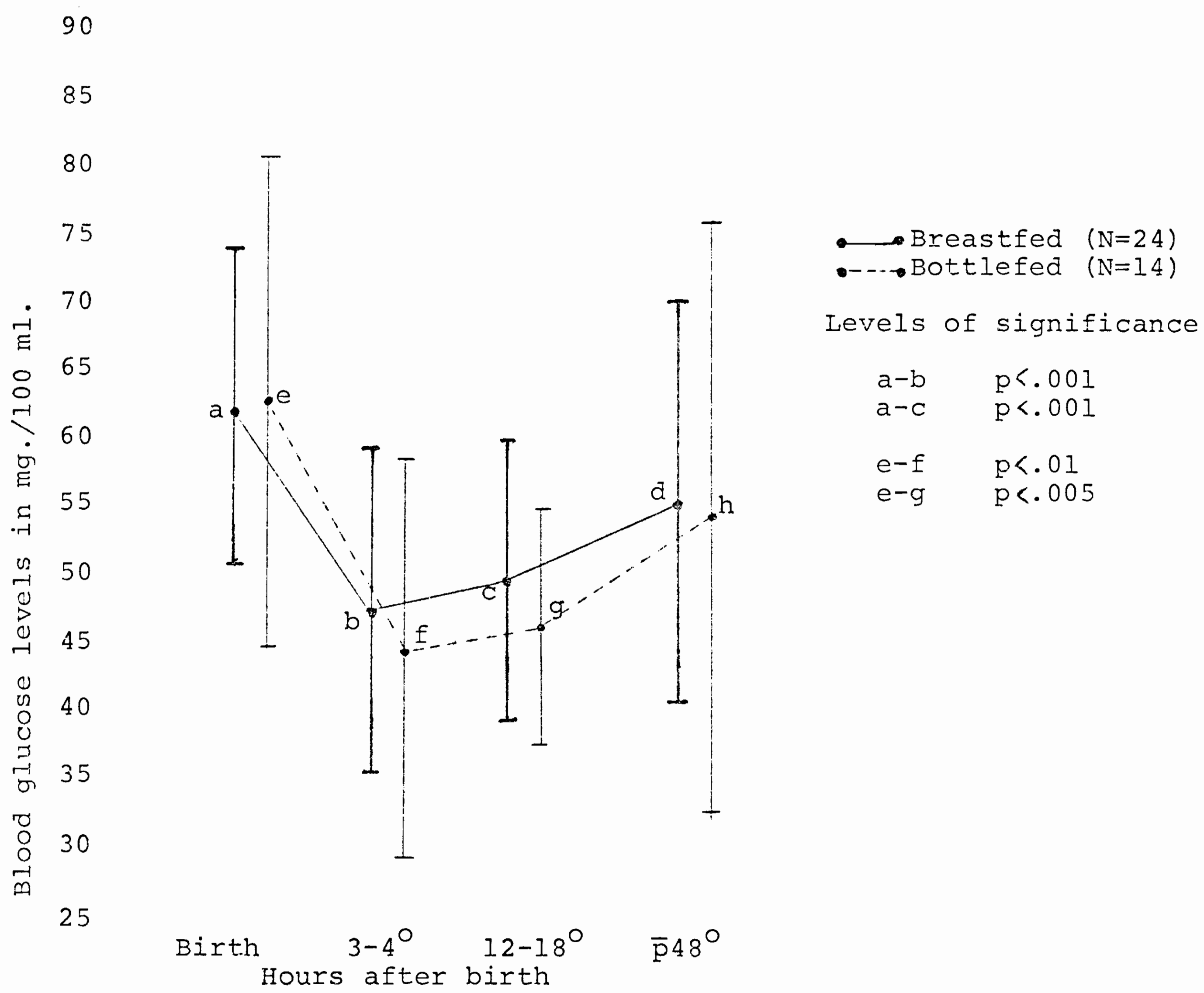

Figure 4. Mean blood glucose levels ±1S.D. of breastfed and bottlefed infants in relation to time after birth.

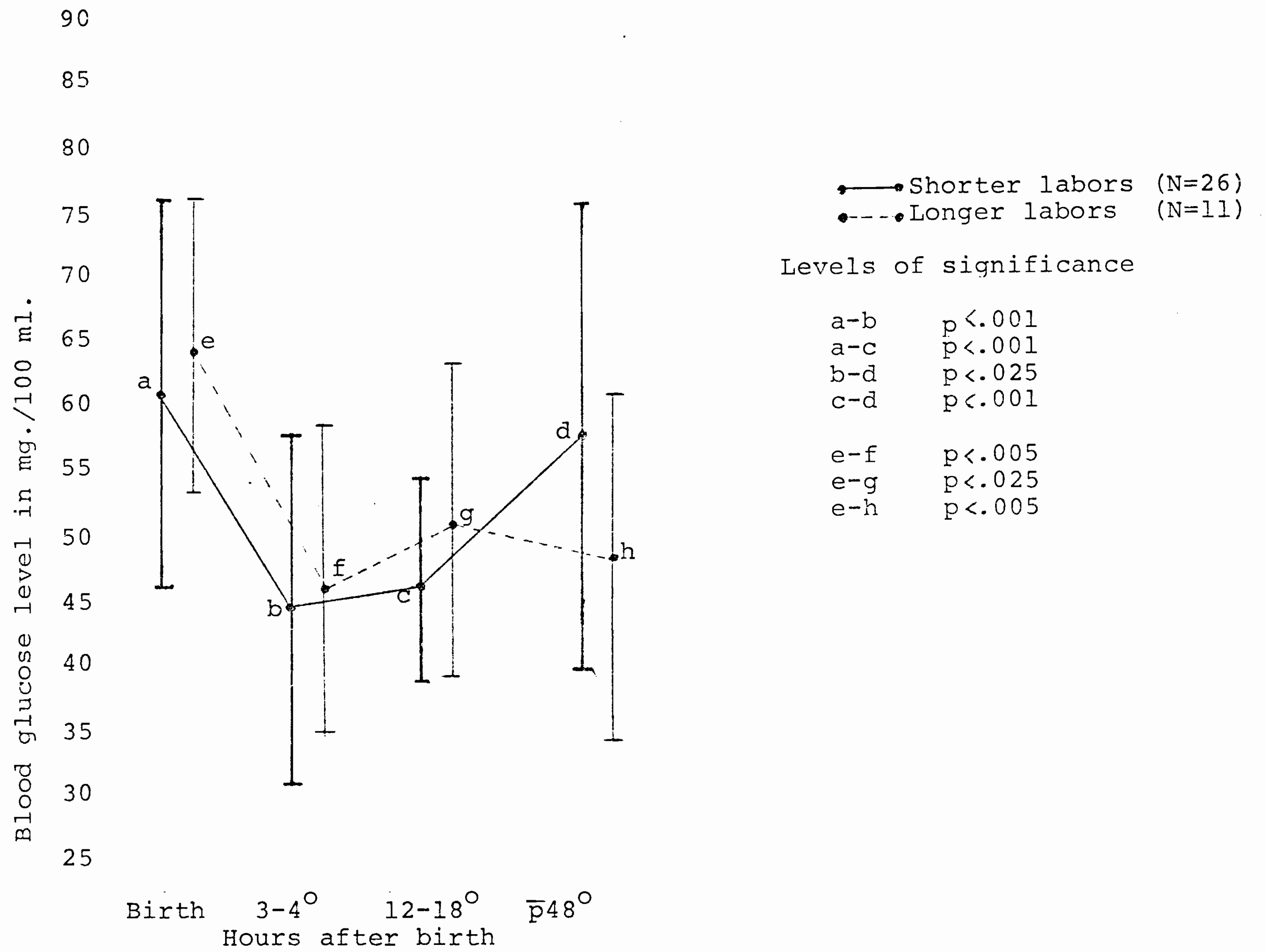

Figure 5. Mean blood glucose levels ±1S.D. for infants born of shorter labors (<7°) and infants born of longer labors (>7°) in relation to time after birth.

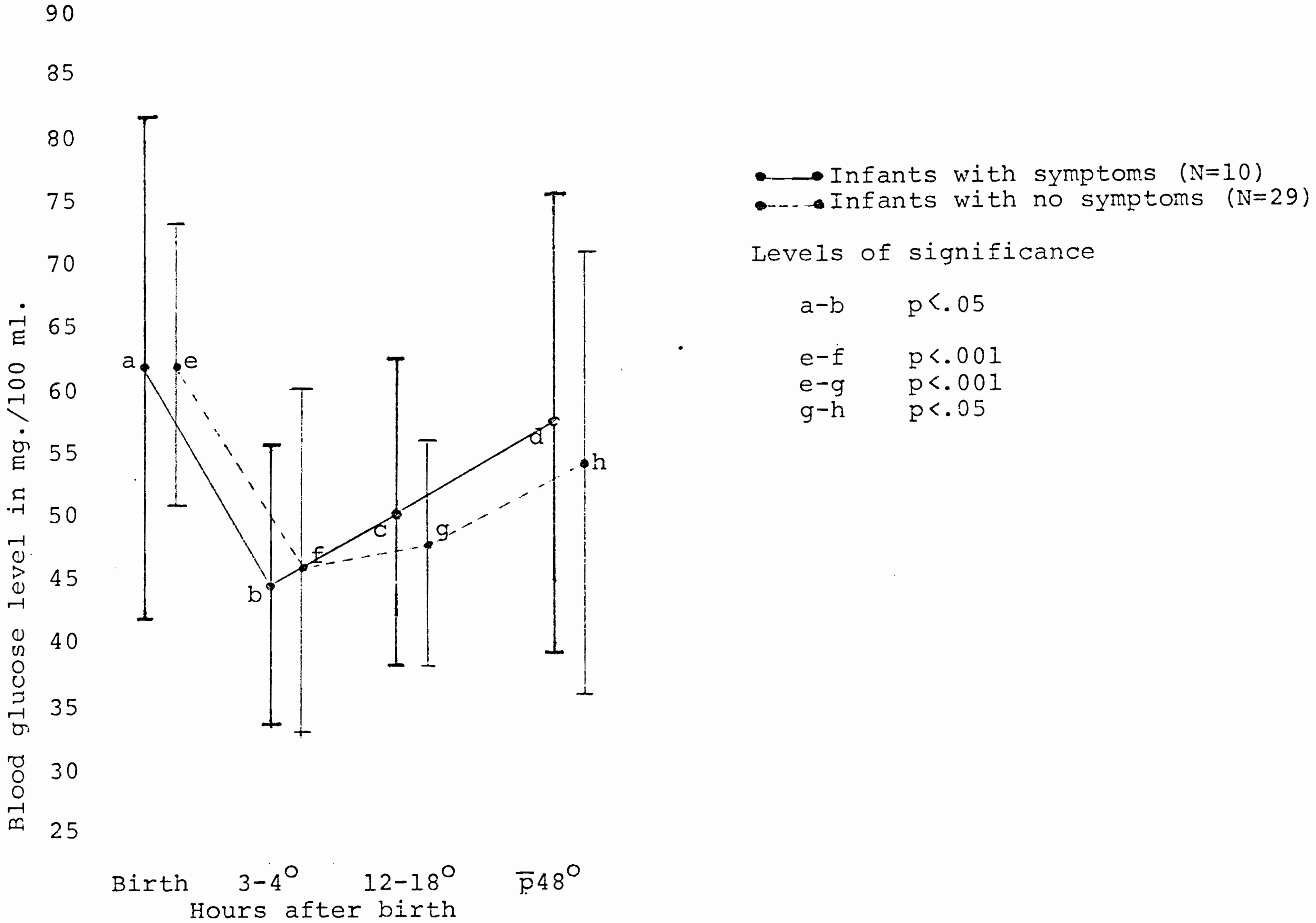

Figure 6. Mean blood glucose levels ±1S.D. for infants with symptoms and infants with no symptoms in relation to time after birth.

Type of feeding and length of labor. (Figure 7). The mean blood glucose levels of both breastfed and bottlefed infants born of mothers with shorter labors follow the general pattern of changes as seen in Figure 1, with the bottlefed infants having slightly lower means after birth. Infants born of mothers with longer labors do not follow the general pattern. Breastfed infants in this group have a decrease in the mean blood glucose level between the 12-18 hour and after 48 hour samples, although this drop is not statistically significant. The bottlefed infants in this group show continual decreases in mean blood glucose levels with the lowest level after 48 hours. The difference between the means of the breastfed - longer labor group and the bottlefed - longer labor group at the after 48 hour sample is statistically significant ($p<.05$). The difference between the means of the bottlefed - shorter labor group and the bottlefed - longer labor group at the same sample is also statistically significant ($p<.05$).

Time of feeding and length of labor. (Figure 8). Infants born of mothers with shorter labors and fed early follow the general pattern of mean blood glucose level changes. Infants born of mothers with longer labors, whether first caloric ingestion occurred before or after 12 hours of age, have a similar pattern of mean blood glucose level change. The means decrease from birth to 3-4 hours, then reverse direction and increase from the 3-4 hour sample until the 12-18 hour sample when a second reverse occurs

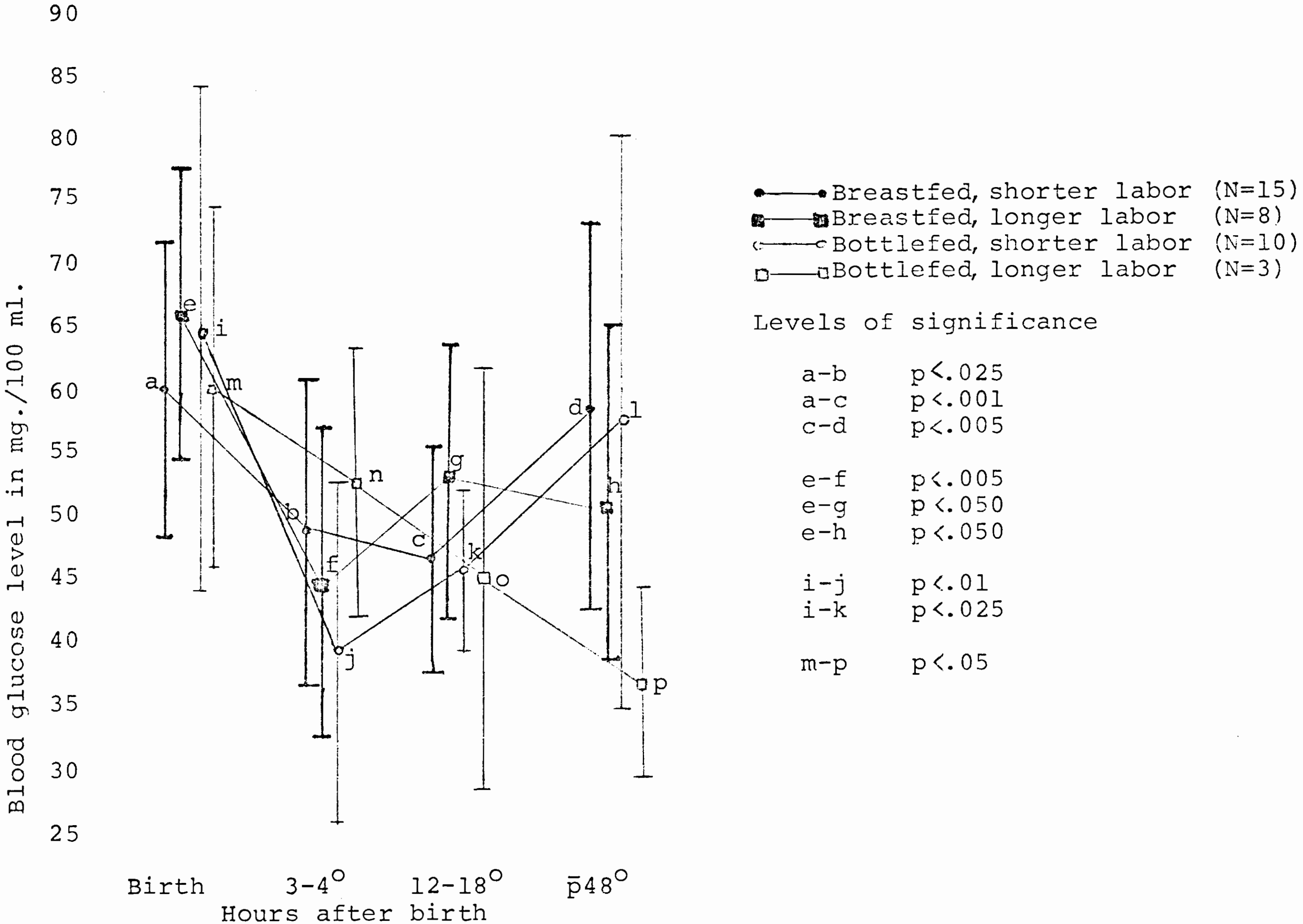

Figure 7. Mean blood glucose levels $\pm$1S.D. for breastfed, shorter labor infants; breastfed, longer labor infants; bottlefed, shorter labor infants; and bottlefed, longer labor infants in relation to time after birth.

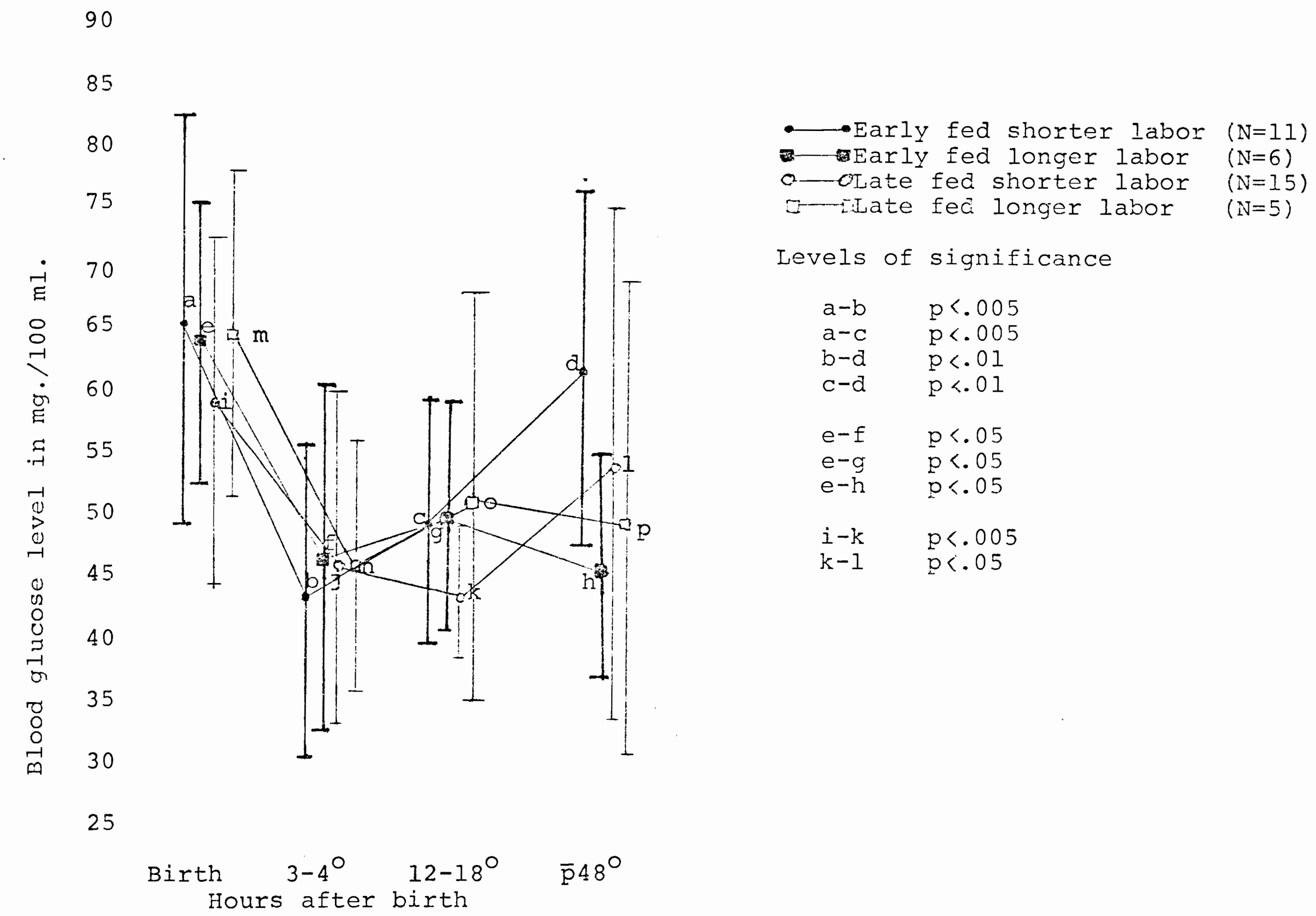

Figure 8. Mean blood glucose levels ±1S.D. for early fed-shorter labor infants, early fed-longer labor infants, late fed-shorter labor infants and late fed-longer labor infants in relation to time after birth.

resulting in a slightly lower mean blood glucose level at the after 48 hour sample. Infants born of mothers with shorter labors and fed late follow the pattern of late fed infants seen in Figure 3 (the reversal of the initial downward trend not occurring until after the 12-18 hour sample.)

Hypoglycemia. Of 149 samples obtained from 39 infants, there were 4 samples (one each from 4 term infants) meeting the criteria established by Cornblath and Schwartz as definitive of hypoglycemia in the neonate (less than 30 mg. per 100 ml. in the term infant in the first three days of life).[17] This represents 2.8% of all samples and 10% of infants in a well neonatal population. Three of the 4 hypoglycemic infants fall in the bottlefed - longer labor category of Figure 7. Figure 9 displays the mean blood glucose levels of these 4 infants.

Correlation of symptoms with hypoglycemia. Correlations of these infants' blood glucose levels with symptomatology and factors previously reported as associated with hypoglycemia (p. 1) were generally not significant. Negative correlations of blood glucose at birth with apathy ($r=-.903$, $p<.05$) and blood glucose at birth with oxygen or positive pressure used for resuscitation ($r=-.903$, $p<.05$) and a positive correlation of blood glucose at 3-4 hours with length of labor ($r=.960$, $p<.05$) were found. Although the number of subjects is so small that no inferences can be made regarding confidence intervals or the accuracy of

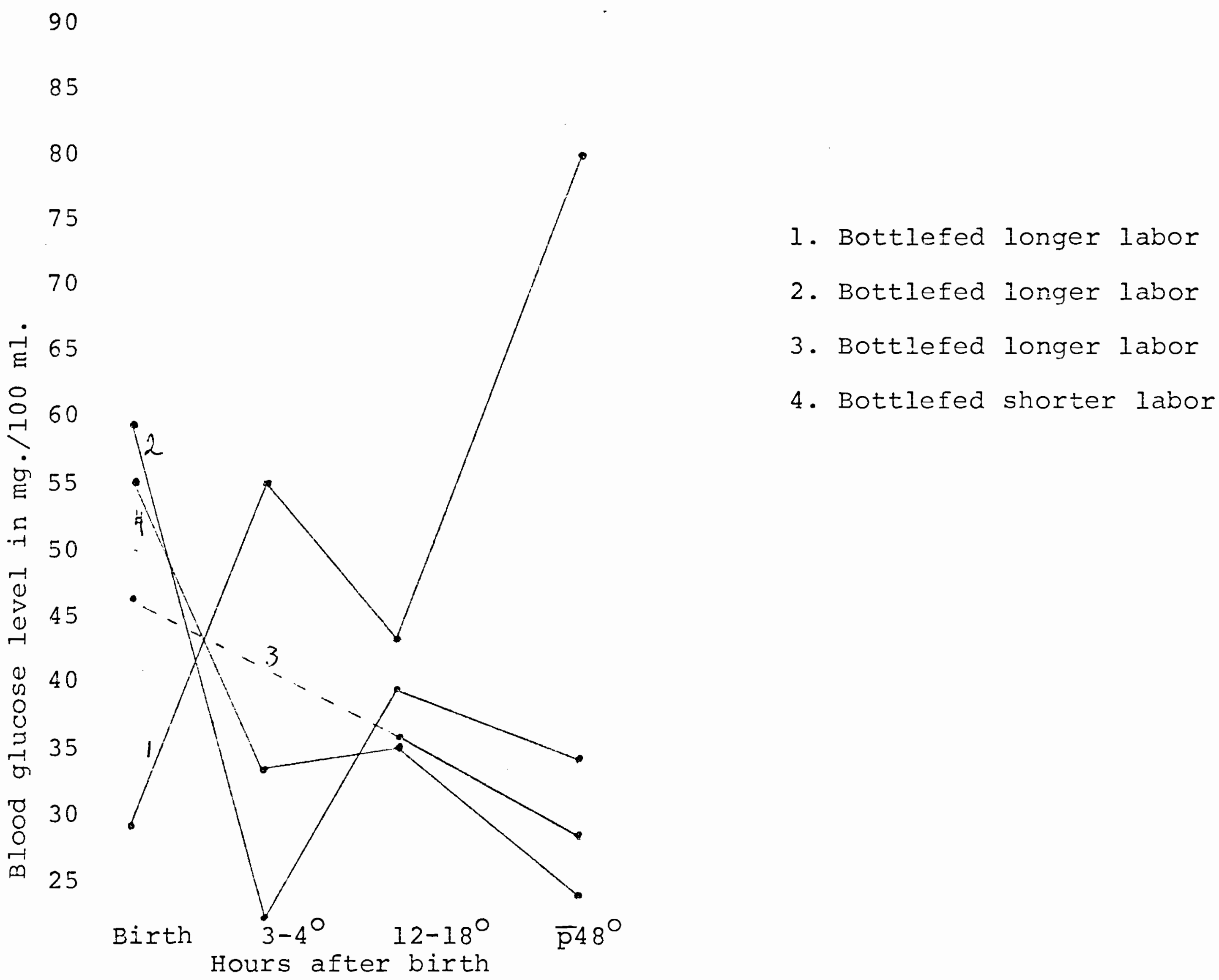

Figure 9. Blood glucose levels of hypoglycemic infants in relation to time after birth (N=4).

these correlations, they should be considered for further study.

Correlation of symptoms and associated factors with blood glucose levels for all 40 infants. For all 40 infants, the infant blood glucose level at birth was positively correlated with the maternal blood glucose level within one half hour of delivery ($r=.800$, $p<.01$). This is to be expected as the infant's level of circulating glucose has been dependent upon the mother's supply.[1,33] However, there was no relationship of either infant blood glucose at birth or maternal blood glucose with subsequent infant blood glucose determinations. A positive correlation was found between the incidence of jitteriness at any time and blood glucose at birth ($r=.347$, $p<.01$). Those infants who exhibited jitteriness showed a mean decrease of 31 mg. per 100 ml. in blood glucose level from the time of birth until 3-4 hours of age. Mean decrease over the same time period for those infants without jitteriness at any time was 17.5 mg. per 100 ml.

There was no correlation between maternal toxemia, maternal weight gain over thirty pounds, length of labor, time from last maternal carbohydrate ingestion to time of delivery, maternal IV during labor, maternal vomiting, infant birth weight-gestational age category, infant Apgar scores or infant fetal heart rates and infant blood glucose levels at any sample time in all 40 infants or for the 4 hypoglycemic infants.

DISCUSSION

There is a general pattern of mean blood glucose level changes, the pattern being a large initial decrease from birth to 3-4 hours, then reversal of the trend with small increases at each subsequent sample. The variations from this pattern are interesting to note. Infants fed after 12 hours of age continue the downward trend in mean blood glucose level until the 12-18 hour sample after which the direction reverses with an increase by the time of the after 48 hour sample (Figure 3). This supports the hypothesis that increased fasting periods may decrease blood glucose levels although an increase in hypoglycemia as defined by Cornblath and Schwartz[17] was not found. Infants born of mothers with longer labors vary from the general pattern by demonstrating a second reversal in direction of change between the 12-18 hour and after 48 hour samples with a decrease in the mean blood glucose level (Figure 5). The amount of change is not statistically significant, but appears worthy of further investigation. No infants were fed before the 3-4 hour sample. It would be valuable to know the pattern of blood glucose level change in infants breastfed or bottlefed frequently from the time of birth.

Although both males and females follow the general pattern of changes in mean blood glucose levels, there is marked difference in the patterns (Figure 2). Males have a greater initial drop and a slow pattern of increase. Although the differences between male and female means after 48 hours is not statistically significant, it does suggest that male infants may have less energy supplying glucose available to them for dealing with stress. Reasons for this difference are not clear.

It is interesting to note the similarity of the mean blood glucose levels in breastfed and bottlefed infants (Figure 4). All bottlefed infants received either Enfamil or Similac, both of which contain lactose as the primary source of carbohydrate; thus whether breastfed or bottlefed, the main source of carbohydrate was the same.

The mean blood glucose levels are most similar for infants with symptoms and infants without symptoms (Figure 6). Symptoms (apathy, cyanosis, high-pitched or weak cry, jitteriness and/or tremors) were present in 11 of 39 infants at some time during the study. In each of these infants, the symptoms were noted during a period of blood glucose drop or at birth (in one infant who was hypoglycemic at birth). These decreases varied form 10-56 mg. per 100 ml. and only once resulted in a hypoglycemic level as defined by Cornblath.[17] While these symptoms may indicate other pathophysiological processes as noted earlier, the occurence of them invariably during a time of blood glucose decrease is indicative of relation to the decrease. No symptoms were noted unaccompanied by blood glucose decreases. There were, however, decreases in blood glucose level not accompanied by symptoms. Eight of the remaining 28 infants experienced decreases of 25-38 mg. per 100 ml. between birth and 3-4 hours of age. Thus, whether or not infants were symptomatic, a number of them experienced larger than usual decreases in mean blood glucose levels. As both symptomatic and asymptomatic infants experienced similar decreases in some cases, the pattern of change for both groups remained similar.

Pagliara[33] has recently suggested that the current definition of clinically significant hypoglycemia should be reevaluated in the absence of large longterm studies of a heterogeneous infant population to substantiate it. These findings of both symptomatic and asymptomatic infants with larger decreases in blood glucose level supports this suggestion. The major unknown factor is the amount of circulating insulin (both of infant and maternal origin) and its relationship to blood glucose levels at intervals during the first days of life. It may be that any useful definition of hypoglycemia may have to take insulin levels as well as glucose levels into consideration. Other important factors needing examination are the presence of other sugars and utilization of sugars (as in cold stress.)

Whether breastfed or bottlefed, the infants born of mothers with longer labors had decreased blood glucose levels after 48 hours after birth. (Figure 7), with bottlefed infants having significantly lower levels. In some way the combination of labor longer than 7 hours with bottlefeeding resulted in the lowest mean blood glucose levels after 48 hours of any category of infants in this study. Whether fed early or late, the infants born of mothers with longer labors demonstrate a slight decrease in mean blood glucose levels between the 12-18 hour and after 48 hour samples (Figure 8). Thus, there is a consistent pattern of decrease in mean blood glucose levels between samples taken at 12-18 hours of age and after 48 hours of age in infants born of mothers with labors longer than 7 hours, whether bottlefed or breastfed, whether fed before or after 12 hours of age. This finding needs investigation in a larger study.

The incidence of hypoglycemia found was lower than expected in view of Lubchenco's expectation that the incidence of hypoglycemia may increase as mandatory fasting time increases.[3] While the incidence did not increase above that found in her study, there was a continual decrease in mean blood glucose level in infants fed after 12 hours of age as previously noted. There were a number of infants with larger drops in blood glucose level with or without symptoms. There is a clear indication of changes in these infants blood glucose levels. It is possible that current feeding patterns result in one more physiological change for these neonates to adapt to, rather than resulting in a supportive supply of available glucose for making other physiological adjustments in the early postnatal period. This is only supposition until the effect of early, frequent, lengthy breastfeeding or other similar feeding patterns upon blood glucose levels are studied.

The population studied may have had an effect upon the incidence of hypoglycemia found in this study. The mothers of these infants were generally middle class women with adequate prenatal care and uncomplicated prenatal and natal courses. This contrasts with Lubchenco's population drawn from as obstetrical service with a higher than average number of complicated obstetrical cases and a primarily medically indigent population.[3] Infants in this study group had mean Apgar scores of 7.2 at one minute and 8.5 at five minutes. There were no SGA infants in the sample and only 4 required the use of positive pressure for resuscitation. The interesting point is that even in a well, low risk population there are hypoglycemic episodes and some infants with larger decreases in blood glucose levels.

SUMMARY

A general pattern of blood glucose level changes following birth has been described. Variations from the general pattern have been identified. These variations and the effect of breastfeeding or other feeding from the time of birth need to be further studied. The question of whether the observed decrease in blood glucose level following birth is a natural phenomenon or is the iatrogenic result of current feeding and general care routines must be considered.

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APPENDIX A

DATA SHEET

Date & time of birth ________________ Hosp.# ______ Subj.# _____

Maternal history

Pregnancy

	Yes	No
Toxemia	______	______
Wt. gain 30#	______	______
Rh sensitization	______	______

LMP ____________________________

Other ____________________________

____

Labor

Time of delivery ________________

Length of labor ________________

Time of last CHO ingestion ________________

Elapsed time to delivery ________________

IV during labor? ________________

Amount & type of IV fluid ________________

Vomiting? ________________

Infant history

FHR during labor 120 ______________

160 ______________

Apgar @1 min. ______ @5 min. ______

Type of resuscitation in delivery room ______________

Gestational age by dates ______________

Gestational age by Dubowitz criteria ______________

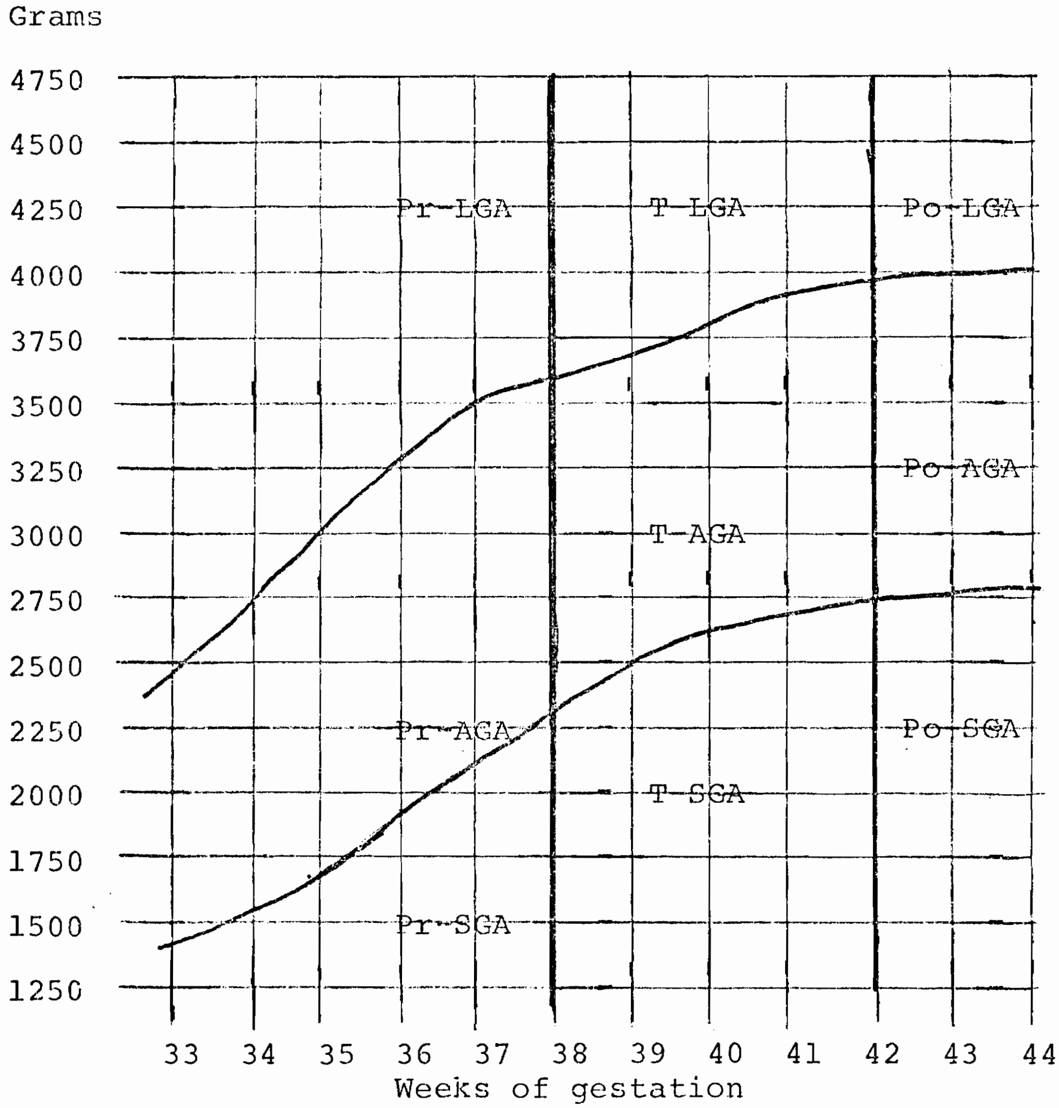
Twin birth? ______________

Anomalies noted ______________

Observations	Yes	No	Time(s)
Apathy	______	______	____________
Apnea	______	______	____________
Cyanosis	______	______	____________
-where?	__________________________________		
Eye-rolling	______	______	____________
Flaccidity	______	______	____________
High-pitched or weak cry	______	______	____________
Hyperactivity	______	______	____________
Jaundice	______	______	____________
Jitteriness	______	______	____________
Seizures	______	______	____________
Tremors	______	______	____________

Other observations:

Birthweight/Gestational Age Classification



Note.-Modified from the University of Colorado Classification of newborns by birthweight and gestational age.

Blood glucose/microhematocrit results

	Exact time	Elapsed time	Blood glucose	Nct.	Nurs. temp.
Birth	______	________	_______________	_____	_______
3-4 hours	______	________	_______________	_____	_______
Time of 1st brst/form	______	________			
12-18 hrs	______	________	_______________	_____	_______
p̄ 48 hrs	______	________	_______________	_____	_______

maternal blood glucose _______________ Time of sample_______

Clinical estimate of gestational age (Dubowitz)

Neurological criteria		External criteria	
Criterion	Score	Criterion	Score
Posture	______	Edema	______
Square window	______	Skin texture	______
Dorsiflexion of foot	______	Skin color	______
Arm recoil	______	Skin opacity	______
Leg recoil	______	Lanugo	______
Popliteal angle	______	Plantar creases	______
Heel to ear	______	Nipple formation	______
Scarf sign	______	Breast size	______
Head lag	______	Ear form	______
Ventral suspension	______	Ear firmness	______
Total	______	Genitals	______
		Total	______

Total both categories_____________

Gestational age read from graph_______________

APPENDIX B

USE OF DATA SHEET

1. Record incidence of toxemia if recorded by physician on prenatal or hospital chart.
2. Record weight gain as reported on chart; if not noted, ask mother.
3. Record Rh sensitization if recorded on chart; if titer levels are available, record them.
4. Record LMP as noted on chart.
5. Record infant history as recorded on chart.
6. If additional room needed for infant observations, record in space for other observations.
7. If jaundice is noted, record degree of jaundice and bili levels if available, in space for other observations.
8. RECORD ALL TIMES IN MILITARY TIME, i.e. 0001-2400.

VITA

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