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Chorionic somatomammotrophin as index of fetal growth

DUNCAN R. MACMILLAN, RUTH HAWKINS, and RONALD N. COLLIER

From the Sections of Pediatric Endocrinology and Neonatology, Department of Pediatrics, University of Louisville School of Medicine, Louisville, Kentucky, U.S.A.

MacMillan, D. R., Hawkins, R., and Collier, R. N. (1976). *Archives of Disease in Childhood*, **51**, 120. **Chorionic somatomammotrophin as index of fetal growth.** Concentrations of chorionic somatomammotrophin (hCS) in maternal plasma at the time of delivery and in placental extracts were determined by radioimmunoassay and related to neonatal growth in 111 normal pregnancies. Mean maternal plasma hCS concentration was lower in association with small-for-dates infants, defined by either height or weight, than with well-grown preterm or term infants. Mean placental hCS concentration was not decreased in association with undergrown infants though placental hCS was correlated with maternal hCS ($r=0\cdot245$).

Chorionic somatomammotrophin (hCS) is a lactogenic protein substance initially identified in placental tissue by Ito and Higashi (1961) and shown by Josimovich and MacLaren (1962) to be immunologically similar to pituitary growth hormone. It is secreted by the placenta almost exclusively into the maternal circulation and very little crosses from the maternal to the fetal circulation (Grumbach *et al.*, 1968). The latter authors do not think that hCS represents a true fetal equivalent of pituitary growth hormone, which is unessential for fetal growth (Blizzard and Alberts, 1956; Reid, 1960; Steiner and Boggs, 1965), but that it produces alterations in maternal metabolism which promote fetal growth indirectly. Our own studies in twins (MacMillan *et al.*, 1973), which showed a strong positive relation between relative twin size and placental hCS concentration, raised the question whether hCS affects fetal growth other than via the maternal circulation.

Maternal serum hCS concentrations rise throughout pregnancy until the last month of gestation, when they tend to level out (Grumbach *et al.*, 1968; Beck, Parker, and Daughaday, 1965; Spellacy, Carlson, and Birk, 1966; Saxena, Emerson, and Selenkow, 1969; Singer, Desjardins, and Friesen, 1970; Samaan *et al.*, 1971; Spencer, 1971; Letchworth *et al.*, 1971; Genazzani *et al.*, 1971). Investigations into the clinical significance of hCS have largely focused on abnormal pregnancies and on the value of maternal serum hCS levels as an 'index of placental function'. Depressed maternal hCS has been related to retarded intrauterine growth associated with high risk pregnancies by Saxena *et al.* (1969), Seppälä and Ruoslahti (1970), Genazzani *et al.* (1971), and Spencer (1971), but there has been no published report of a specific study of maternal serum hCS levels as an index of fetal growth, relating hCS to both weight and length of the newborn in uncomplicated pregnancies. Letchworth *et al.* (1971), however, showed a significant relation between maternal hCS and birthweight in their study of normal pregnancies, but they did not examine birth length.

Maternal serum concentrations of hCS fluctuate irregularly during pregnancy (Vigneri *et al.*, 1975) and after the onset of labour may rise abruptly (Singer *et al.*, 1970) or fall (El-Tomi, Crystle, and Stevens, 1970). Some of the difficulty in relating maternal hCS to infant birthweight has been attributed to these fluctuations (Genazzani *et al.*, 1971). The present study was undertaken to assess more fully the relation of the growth of the newborn infant to maternal hCS levels at the time of delivery. The relation of placental hCS to maternal hCS levels and to fetal growth was also examined.

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Patients and methods

The 111 mothers studied were all delivered in the obstetrics unit of the Louisville General Hospital, a hospital serving a largely inner city population. Mothers with evidence of eclampsia, pre-eclampsia, diabetes, Rh isoimmunization, and postmaturity were excluded. Maternal venous blood was obtained from an antecubital vein as soon as possible after delivery and before delivery of the placenta. Blood was collected in a heparinized tube, centrifuged promptly, and the plasma separated and placed in a freezer along with the corresponding placenta at −20 °C. Before assay for hCS the frozen placenta was thawed at 4 °C for 12 hours, membranes and cord were trimmed away, the wet placental weight obtained, and the entire placenta was then homogenized in a Waring blender. Weighed aliquots of homogenized placenta were lyophilized.

A placental extract was obtained by a single extraction of 10 mg lyophilized placental powder with 5 ml 0·3 mol/l potassium chloride. Both plasma and placental extracts were radioimmunoassayed by a double antibody technique using hCS tagged with ^{131}I. Each sample was run in duplicate multiple dilutions against a Friesen placental lactogen standard. Maternal plasma hCS concentration (MathCS) and placental hCS concentration (PlachCS) were determined by computerized parallel-line assay. Total placental hCS content (TPhCS) was derived from PlachCS and placental weight. Infant lengths used were the mean of three consecutive measurements during the first 24 hours of life using a measuring frame. Lengths and weights were plotted on Colorado Intrauterine Growth Charts (Lubchenko *et al.*, 1963). Gestational age was calculated solely from the last menstrual period.

From their weight and calculated gestational age the infants were arbitrarily classified as (*a*) controls, if weight was at or above the 10th centile and gestation was 36 to 40 weeks; (*b*) small-for-dates (SFD), if weight was below the 10th centile and gestation was 36 to 40 weeks; or (*c*) normal preterm, if weight was at or above the 10th centile and gestation was 28 to 35 weeks. No infants of less than 36 weeks' gestation with weight below the 10th centile were seen during the period of study.

Infants were similarly categorized on the basis of length and gestational age except that the 25th centile was used to delineate the SFD group. By these criteria 5 infants fell into a preterm SFD group but, because of the small number, were not subject to analysis as a group.

Results

A matrix of correlation coefficients between maternal, infant, and placental variables in the group of 111 cases is presented in Table I. Expected inter-relation between gestational age, birthweight, birth length, and placental weight were found. However, none of the hCS functions correlated significantly with these 4 variables over the gestational range 28–40 weeks. A significantly positive correlation between MathCS and PlachCS was seen ($r=0·245$, $P<0·01$). There was a similar relation between TPhCS and MathCS but no significant correlation of MathCS with placental weight alone.

Means and standard deviations for 7 maternal, infant, and placental variables for the 111 infants categorized as preterm, SFD, or control on the basis of birthweight and calculated gestational age are shown in Table II. Similar information is provided in Table III for 106 infants categorized on the basis of birth length and gestational age.

Low mean MathCS was seen in the SFD group, categorized by either weight or length, with the differences in MathCS between the SFD and premature group and the SFD and control group being highly significant. Group differences in mean PlachCS and TPhCS were not significant.

Discussion

The correlation of MathCS with PlachCS, a relation not previously documented, is a finding of considerable importance in support of the validity of PlachCS as a function of placental hCS production. In this study MathCS bears a closer relation

TABLE I

Correlation matrix for maternal, newborn, and placental variables

	Gestation	Weight	Length	Placental weight	PlachCS	TPhCS	MathCS
Gestation	—	0·571*	0·663*	0·182	−0·008	−0·024	−0·046
Weight	0·571*	—	0·690*	0·438*	0·028	0·096	−0·020
Length	0·663*	0·690*	—	0·350*	−0·024	−0·007	−0·044
Placental weight	0·182	0·438*	0·350*	—	−0·100	0·150	0·041
Placental hCS	−0·008	0·028	−0·024	−0·100	—	0·853*	0·245†
TPhCS	−0·024	0·096	−0·007	0·150	0·853*	—	0·230†
Maternal hCS	−0·046	−0·020	−0·044	0·041	0·245†	0·230†	—

*r significant $P<0·001$; † r significant $P<0·01$.

TABLE II

hCS and mean (±SD) growth measurements in infants grouped according to gestation and birthweight

	Gestation (weeks)	Birthweight (g)	Birth length (cm)	Placental weight (g)	PlachCS (mg/g dry wt)	TPhCS (g)	MathCS (μg/ml)
Control (n=46)	37·3±1·6	2484·4±403·8	46·9±2·8	405·2±82·2	25·5±15·4	1·7±1·0	4·3±2·8
SFD (n=26)	37·7±1·4	2018·5±276·8	44·6±2·6	342·7±91·3	25·6±16·9	1·5±1·5	3·0±2·2*
Preterm (n=39)	32·9±2·2	1933·7±338·0	44·0±3·1	366·0±91·3	27·4±13·1	1·7±0·9	5·4±4·0

* Differs significantly from both preterm infants ($P<0·01$) and controls ($P<0·01$).

TABLE III

hCS and mean (±SD) growth measurements in infants grouped according to gestation and birth length

	Gestation (weeks)	Birthweight (g)	Birth length (cm)	Placental weight (g)	PlachCS (mg/g dry wt)	TPhCS (g)	MathCS (μg/ml)
Control (n=42)	37·6±1·6	2509·1±406·5	47·9±2·1	406·9±78·3	24·1±14·4	1·5±0·9	4·4±2·7
SFD (n=30)	37·2±1·4	2045·9±283·3	43·5±1·8	348·6±95·9	27·5±17·7	1·7±1·5	2·9±2·3*
Preterm (n=34)	32·7±2·3	1937·3±356·5	44·3±3·1	364·4±97·7	26·5±12·5	1·6±0·9	5·6±4·2

* Differs significantly from both preterm infants ($P<0·005$) and controls ($P<0·01$).

to PlachCS than to placental weight. Stronger correlations between MathCS and placental weight have been found when maternal blood is sampled before the onset of labour (Saxena *et al.*, 1969; Seppälä and Ruoslahti, 1970; Genazzani *et al.*, 1971; Lebech and Borggaard, 1974), in contrast to the inconsistent relations seen in this study and in those of Spellacy *et al.* (1966) and Samaan *et al.* (1971) after the onset of labour. A more impressive MathCS—PlachCS relation may also exist if MathCS is sampled before labour but this remains to be explored.

The lack of correlation of MathCS with gestational age may seem inconsistent with the studies of hCS during pregnancy previously cited, but most mothers in our study were at 36 to 40 weeks' gestation, when MathCS levels should have reached a plateau. In the type of analysis illustrated in Table I no attempt is made to correlate hormonal influences with the appropriateness of fetal growth for gestational age, since raw growth data uncorrected for gestational age are used. The data in Tables II and III do reflect the relation of hCS to the adequacy of fetal growth relative to gestational age. The significantly lower MathCS for newborns defined as small for gestational age by weight is consistent with the observations of Letchworth *et al.* (1971), also in normal pregnancies. Other studies not specifically examining pregnancies at risk for placental insufficiency have failed to show this relation (Sciarra *et al.*, 1968; Spellacy *et al.*, 1966; Singer *et al.*, 1970) except for a low but significant correlation between MathCS and infant weight found in unselected pregnancies by Cramer, Beck, and Makowski (1971).

Differences in mean MathCS in our study are more striking than those found by the above authors. However, the greater variability encountered in our values, possibly related to the onset of labour, tends to decrease somewhat the significance of the differences. The relation of birth length to MathCS is impressive, particularly considering the greater potential for error in this growth measurement. Though the criterion for SFD by length (25th centile) was less stringent than that for weight (10th centile), the population studied was generally underweight for length by the Colorado standards and those in the SFD-by-length group deviated from their controls in length and weight to a similar degree.

Placental insufficiency occurring late in gestation could produce the decreased MathCS and low infant birthweight seen in the SFD groups, but a depression in mean weight out of proportion to the affect on length would be expected. The low birth length of the SFD groups is more consistent with protracted suboptimal hCS secretion either as an isolated phenomenon or as a component of impaired general placental function. This interpretation contrasts with the commentary of Gruenwald (1974), who questioned placental dysfunction as a factor in abnormal fetal growth and development. However, maternal factors may well represent the primary influence on both

MathCS and fetal growth with placental pathology playing a minor role in the growth alterations seen. It remains to be seen whether maternal undernutrition, for example, adversely affects fetal growth by a simple effect on maternal metabolism or whether a reduction in placental size or function must also occur. To date, the only maternal metabolic alteration known to depress MathCS is hyperglycaemia (Burt, Leake, and Rhyne, 1970; Gaspard, Sandront, and Luyckx, 1974). The possibility that the poor quality, high carbohydrate diets of inner city mothers could affect hCS production should be explored.

While no significant differences in PlachCS or TPhCS between the three groups were seen, inaccuracies in determining gestational age may obscure a relation between fetal growth and PlachCS. We found in twins (MacMillan *et al.*, 1973) a significant relation between newborn length, weight, and PlachCS, but only under the conditions of intra-pair comparison where factors such as gestation, maternal health, and genetic endowment are controlled.

From these observations we suggest that hCS represents an important though indirect hormonal influence on fetal growth, possibly independent of general placental function. While further study of the effects of the maternal environment on fetal growth is essential, the placenta must remain a focal point in attempts to understand the metabolic processes affecting intrauterine growth.

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Correspondence to Dr. D. R. MacMillan, Department of Pediatrics, University of Louisville School of Medicine, Health Sciences Center, P.O. Box 1055, Louisville, Kentucky 40201 U.S.A.