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Human chorionic somatomammotropin, estriol and oxytocinase as indexes of fetal growth

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1 Introduction

The increasing interest to reduce perinatal morbimortality rates has stimulated the search for adequate and effective methods for assessing fetal growth and wellbeing in high risk pregnancies.

Several biochemical, biophysical and clinical methods have been suggested to allow a better evaluation of the fetus.

Good fetal vitality will result in a vigorous neonate with an adequate birthweight. This will depend on good placental function, normal fetal growth and the presence or absence of fetal distress.

With the aim of obtaining reliable fetal growth indicators, the following determinations have been performed:

1. Human chorionic somatomammotropic hormone (hCS) which reflects the trophoblast endocrine functions [24] and may play a role in fetal growth [26].
2. Estriol, synthetized by the feto-placental unit [5], the levels of which reflect fetal adrenal and placental functions and the metabolic exchange between fetal and placental compartments.
3. Oxytocinase. The maternal levels of this enzyme, produced by the sincitiotrophoblast, may reflect functional placental mass [13].

2 Material and Methods

A group of 56 women with high risk pregnancies were studied since the 32nd week of gestation. The associated maternal diseases are shown in Tab. I.

Curriculum vitae

GUSTAVO GIUSSI *was born in Montevideo, Uruguay, in 1943. He graduated as Medical Doctor from the School of Medicine, University of Uruguay, in 1971. 1973–1975 WHO research fellow at the training course on Biology of Reproduction, Universidad del Salvador, Buenos Aires, Argentina. At present, Head of the Biochemical Laboratory of the Latin American Center of Perinatology and Human Development (PAHO/WHO), Montevideo, Uruguay. Current work is centered on Perinatal Endocrinology.*

The cases with arterial hypertension were those with diastolic blood pressure of 90 mm Hg or higher. Diabetic patients were classified according to WHITE [30].

When patients were Rh (-) and had a positive agglutinin title they were considered Rh isoimmunization.

In the group of other diseases were included patients with cardiac disease, urinary infection, intrauterine growth retardation and epilepsy.

Serum hCS, estriol and oxytocinase levels were compared among the different maternal groups. The variance analysis did not show statistical differences between these diseases.

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Tab. I. 56 women with high risk pregnancies. Studied since the 32nd week of gestation with the associated maternal diseases.

Maternal Diseases	hCS	Estriol	Oxytocinase
Hypertension	7	7	6
Diabetes B and C	7	7	6
Diabetes D-F-R	4	4	4
Diabetes + Hypertension	3	4	4
Rh isoimmunization	10	9	8
Rh isoimmunization + Hypertension	1	1	0
Rh isoimmunization + Diabetes	2	2	1
Other diseases	22	21	13
TOTAL	56	55	42

Patients who had received drugs (e.g. ampicillin, nitrofurane, sulfamides, corticoids, etc.) that could alter hormonal levels, were not included in this study.

In all patients, three blood samples were obtained weekly, at the same time (11:30 to 12:00 am) to avoid circadian variations. The serum was separated and kept at −20 °C until it was processed. **Only the average value of the three samples obtained in the week preceding delivery was considered for this study.**

hCS was determined by a specific RIA with commercial kits [16]*.

Immunoreactive estriol was determined by RIA in unextracted serum. Commercial kits were used [9]**.

Oxytocinase activity was determined by a colorimetric method, using L-cystine-di-B-naftilamide as substrate [29].

All newborns were weighed using the same scale and during the first hour of life. Gestational age was calculated by weeks of amenorrhea and confirmed by the score of CAPURRO [2].

Newborns were considered small for date when their weight was below the 10th percentile of the local growth curve [3] (Fig. 1).

The newborns were classified into two groups, small for date and adequate weight for gestational age. The mean gestational age in the small for date group was 268 ± 13.7 days ($\bar{X}$ ± 1 SD) and in the adequate weight group, 274.3 ± 14.4 days ($\bar{X}$ ± 1 SD). The difference between both groups was not statistically significant (t test).

3 Results

3.1 hCS, estriol and oxytocinase levels related with birthweight.

The mean level of hCS obtained during the week preceding delivery was correlated with the weight of the newborns. There was a weak association between both variables ($r = 0.30, p < 0.05$) (Fig. 2). Serum estriol levels obtained in 55 pregnancies were correlated with the weight of the newborns.

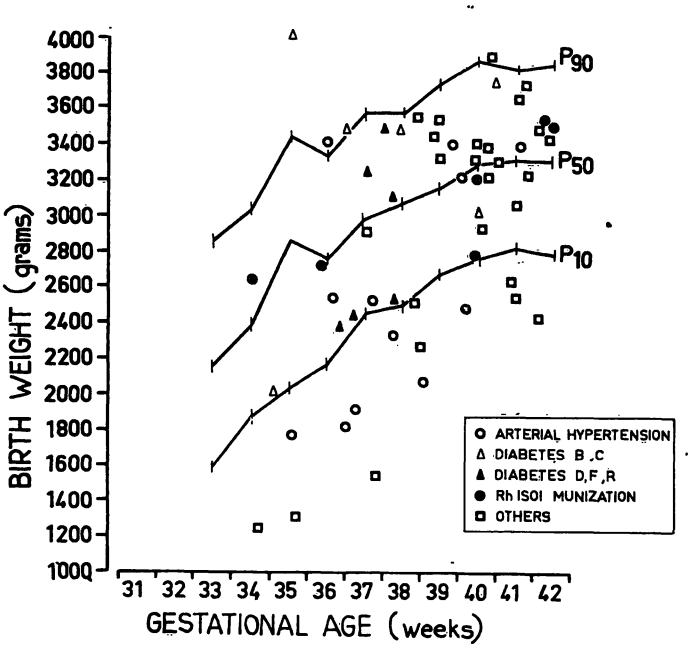

Fig. 1. Local growth curve percentiles 10, 50 and 90. All neonates are plotted according to maternal disease.

* HPL Immunoassay Kit Code IM. 68
Amersham, 2636 S. Clearbrook Drive, Arlington Heights Ill. 60005, EE. UU.

** Estriol Serum (extracted or direct) and urine RIA test kit. Nuclear Medical Systems, Inc., 1531, Monrovia Ave., Newport Beach, CA 92663, EE. UU.

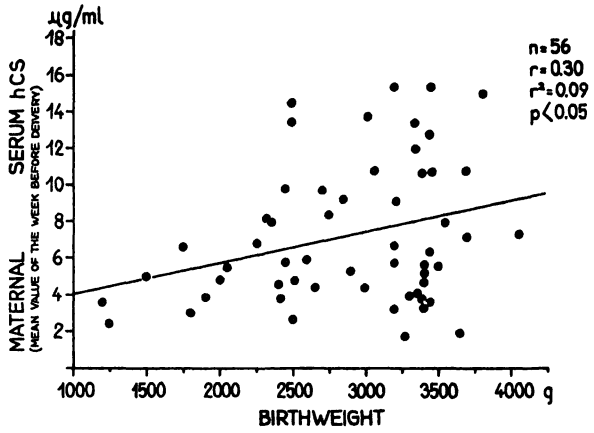

Fig. 2. Correlation between mean maternal hCS during the week before delivery and neonatal birthweight in high risk pregnancies.

A weak correlation was found ($r = 0.33$, $p < 0.01$) (Fig. 3).

Oxytocinase levels were determined only in 42 patients. The correlation between these levels and birthweight was weak ($r = 0.30$, $p < 0.05$) (Fig. 4).

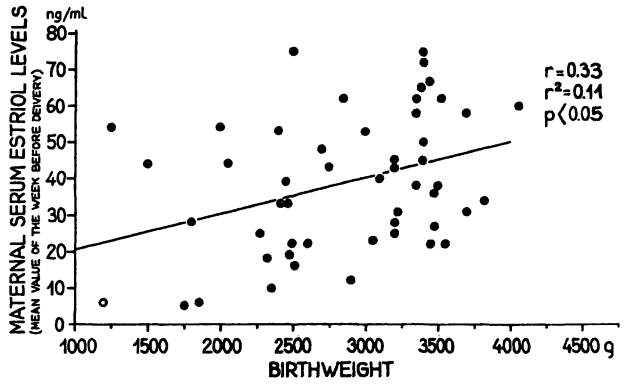

Fig. 3. Correlation between mean maternal serum estriol during the week before delivery and neonatal birthweight in high risk pregnancies.

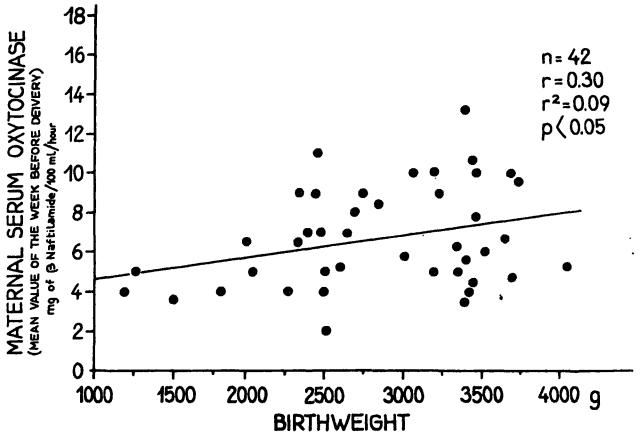

Fig. 4. Correlation between mean maternal serum oxytocinase during the week before delivery and neonatal birthweight in high risk pregnancies.

3.2 hCS, estriol and oxytocinase levels according to birthweight (small for date and adequate weight).

hCS. Maternal hCS level corresponding to 42 newborns with adequate birthweight for their gestational age was 7.94 ± 3.98 ug/ml ($\bar{X}$ ± 1 SD). This value was statistically higher (t test, $p < 0.05$) than the corresponding to the group of 14 small for date newborns, which was 5.15 ± 2.11 ug/ml ($\bar{X}$ ± 1 SD) (Fig. 5).

Based on this difference, a critical level of 7 ug/ml was arbitrarily established. In 12 of 33 pregnancies (36.4%) with levels of 7 ug/ml or less of hCS in serum, newborns were small for their gestational age.

On the other hand, when serum hCS level was higher than 7 ug/ml, only 2 of 23 newborns (8.7%) were small for date.

The difference between both groups was statistically significant (FISHER test, $p = 0.015$) (Fig. 6).

Estriol. The mean value of maternal estriol in serum was compared between 37 adequate weight newborns (42.38 ± 18.55 ng/ml) and 14 small for dates (29.24 ± 16.75 ng/ml). A statistically significant difference was found between both groups (t test, $p < 0.05$) (Fig. 7).

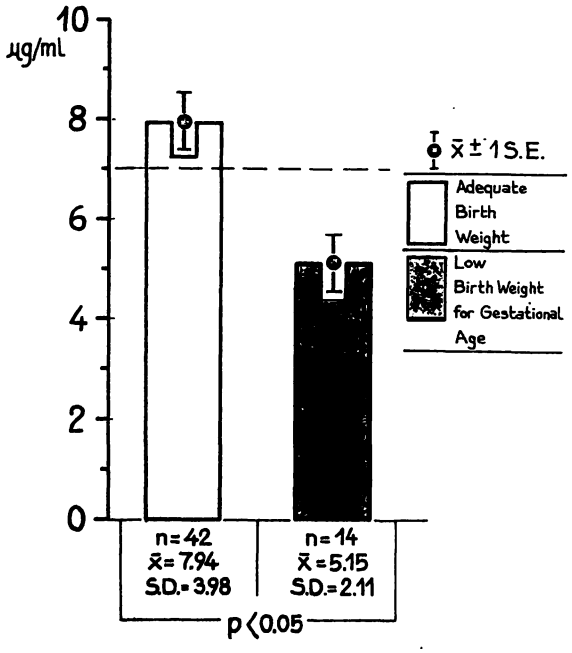

Fig. 5. Mean maternal hCS values obtained the week before delivery for both groups, small-for-date and adequate weight neonates.

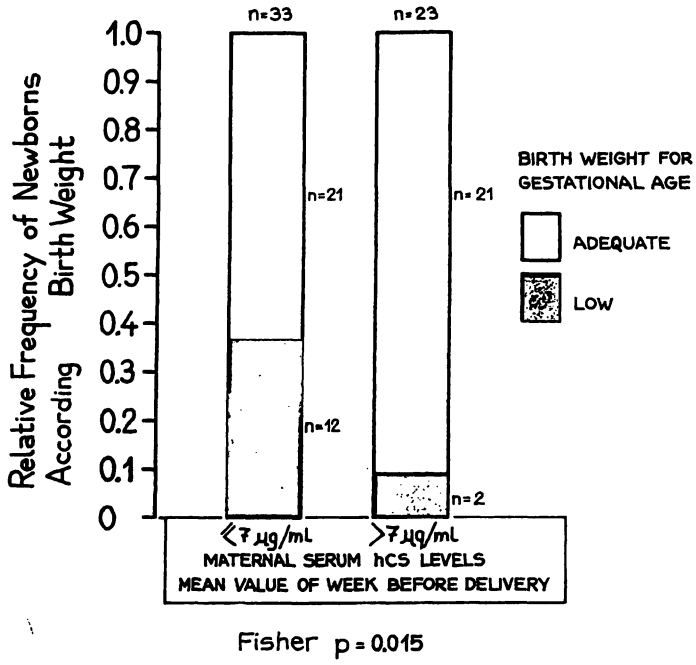

Fig. 6. Relative frequency of neonates classified according to birthweight for the gestational age and to critical value of maternal serum hCS.

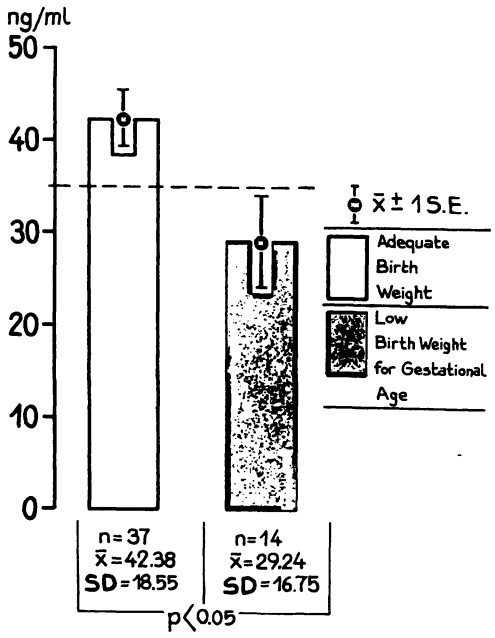

Fig. 7. Mean maternal estriol values obtained the week before delivery for both groups, small-for-date and adequate weight neonates.

Based on this difference, the arbitrary value of 35 ng/ml was established as critical level for serum estriol.

In 9 of 23 pregnancies (39.1%) with serum estriol of 35 ng/ml or less, the newborns were small for date. On the other hand, when the serum estriol level was more than 35 ng/ml, only 5 of 28 neonates (17.9%) were small for dates.

This difference was not statistically significant (FISHER test, p = 0.06) (Fig. 8).

Oxytocinase. A similar analysis between both groups of adequate weight and small for date neonates was performed with the mean level of oxytocinase. There was no statistically significant difference (t test, $p > 0.05$). However, oxytocinase levels were higher in the group of mothers with adequate weight newborns (7.10 ± 2.53 mg B-naftilamide/100 ml/hr) than in the group of mothers with small for date neonates (5.74 ± 2.41 mg B-naftilamide/100 ml/hr).

3.3 hCS and estriol studied jointly as indicators of possible newborn weight (small for date or adequate weight).

Critical hCS and serum estriol levels were considered jointly (7 ug/ml and 35 ng/ml respectively). Neonates were divided into two groups: One group from mothers with both hormones below the critical levels, and the other from mothers in whom both values were above this level.

In the group of mothers with levels below the critical value, 8 of 13 neonates (61.5%) were small

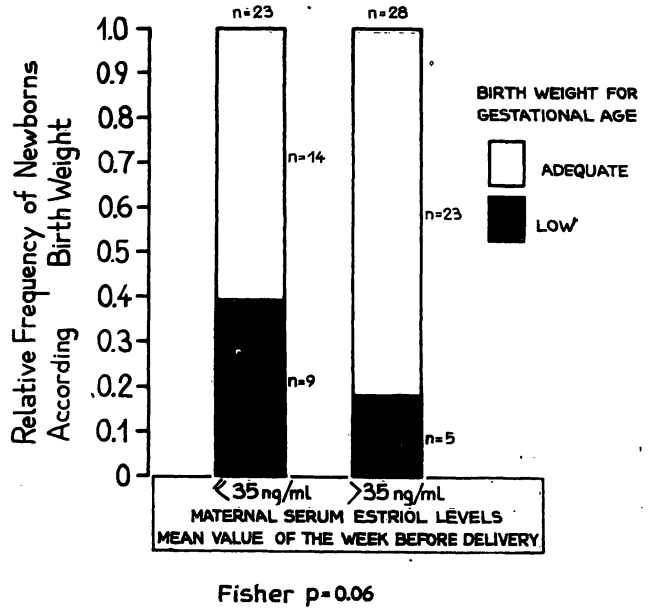

Fig. 8. Relative frequency of neonates classified according to birthweight for the gestational age and to the critical value of maternal serum estriol.

for date; on the other hand, when hormone levels were above the critical level, only 1 of the 13 newborns (7.7%) was small for date. The difference between both groups was statistically significant (FISHER test, p = 0.005).

In 26 mothers in whom both hormone levels were above or below critical values, the correct prediction of adequate weight or small for date was made in 20 (76.9%) (Fig. 9).

From the total number of 51 patients studied, 26 (51%) had both hCS and estriol levels either above or below critical values. In 10 patients (19.6%) hCS was above and estriol was below critical values. In 15 pregnancies (29.4%) the reverse situation was found (Fig. 10).

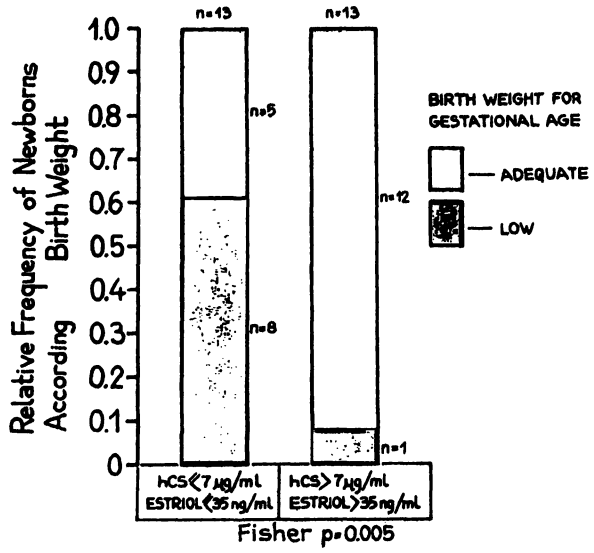

Fig. 9. Neonate distribution according to the birthweight for gestational age when critical levels of both hormones were considered concomitantly.

4 Discussion

Several authors have found an association between birth-weight and maternal serum levels of hCS, estriol and oxytocinase [1, 8, 10, 11, 12, 14, 15, 16, 17, 18, 20, 21, 22, 23, 25, 28].

However, this association was not confirmed by others [4, 6, 7, 19, 27]. **Although we have found statistically significant correlations between these parameters in our population, their dispersion was considerable.**

When we divided our newborns into two groups, one of small for dates and the other with adequate birthweight, **maternal serum levels of hCS and estriol were significantly lower in those with small for date newborns.** On the other hand, **there was no statistically significant difference when only oxytocinase serum levels were studied.**

A critical level of maternal serum hCS and estriol was established according to the above results, below which newborns would have a greater possibility of being small for date.

Approximately 30% of the newborns with maternal hCS serum levels equal or lower than 7 ug/ml were small for date. A similar incidence of small for dates was observed when maternal serum estriol levels were lower than 35 ng/ml.

However, **a greater proportion of false negatives (18%) (small for dates with high hormonal levels)**

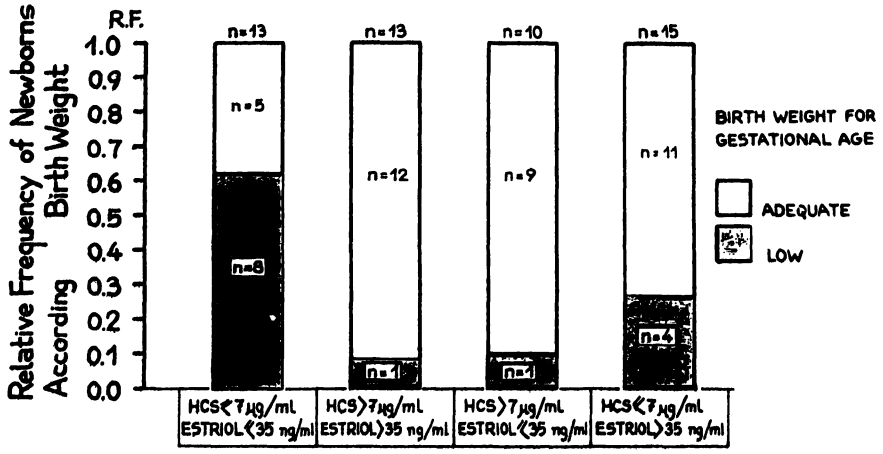

Fig. 10. Neonate distribution according to the birthweight for gestational age considering that hCS and maternal estriol levels were above or below critical values.

was observed with estriol than with hCS, whose incidence of false negatives was 8.7%.
When both hormones were considered simultaneously, in 50% of the patients, both levels were either high or low. The prediction of birthweight was correct in 77% of these cases (Fig. 9). Only one of these 26 pregnant women (3.8%) had a small for date newborn and higher than critical maternal hormone levels.
Summarizing, **our results indicate that fetal growth can be better predicted by the concomitant consideration of hCS and estriol levels in maternal serum than by studying each hormone separately.**

5 Summary

A group of 56 women with high risk pregnancies were studied since the 32nd week of gestation.
With the aim of obtaining reliable fetal growth indicators, maternal serum hCS, estriol and oxytocinase levels were determined. hCS and estriol were determined by specific radioimmunoassays and oxytocinase with a colorimetric method.
Mean values obtained the week before delivery of both hormones and the enzyme were correlated with the weight of the newborns. The correlation coefficients were 0.30, 0.33 and 0.30 for hCS, estriol and oxytocinase respectively (Figs. 2, 3 and 4).
The newborns were classified into two groups, small for date and adequate weight for gestational age. Maternal hCS level corresponding to newborns with adequate birthweight for their gestational age was 7.94 ug/ml. This value was statistically higher than that corresponding to the group of small-for-date newborns, which was 5.15 ug/ml (Fig. 5).
Similar results were obtained when the maternal estriol levels were considered according to the birthweight (Fig. 7). The same analysis applied to **oxytocinase values did not show statistically significant differences.**
Arbitrary critical levels were established for hCS and estriol at 7 ug/ml and 35 ng/ml respectively. When values were below these levels, newborns would have greater possibility of being small for dates (Figs. 6 and 8).
The predictive value was best when both hormones were considered concomitantly (77%) (Fig. 9). These results indicate the suitability of considering hCS and estriol levels in order to assess fetal growth.

Keywords: Adequate-weight newborn, fetal growth, high risk pregnancies, serum estriol, serum hCS, serum oxytocinase, small-for-date newborn.

Zusammenfassung

HCS, Östriol und Oxytozinase als Indices des fetalen Wachstums.
Eine Gruppe von 56 Risikoschwangeren wurden seit der 32. Schwangerschaftswoche beobachtet. Mit dem Ziel, zuverlässige fetale Wachstums-Indikatoren zu erhalten, wurden HCS, Östriol und Oxytozinase im Serum bestimmt. HCS und Östriol wurden durch spezifische Radioimmunoassays und Oxytozinase durch eine kolorimetrische Methode bestimmt.
Die in der Woche vor der Entbindung erhaltenen Mittelwerte von beiden Hormonen und dem Enzym wurden zu dem Gewicht der Neugeborenen in Beziehung gebracht. Die Korrelations-Koeffizienten waren 0.30, 0.33 und 0.30 für das HCS, Östriol und Oxytozinase (s. Abb. 2, 3 und 4).
Die Neugeborenen wurden in zwei Gruppen eingeteilt: die Untergewichtigen und die Normalgewichtigen gemäß ihres Schwangerschaftsalters. Der mütterliche HCS-Spiegel in der Gruppe der Neugeborenen mit normalem Geburtsgewicht gemäß ihrer Schwangerschaftszeit war 7,94 µg/ml. Dieser Wert war statistisch höher als der entsprechende der Gruppe der untergewichtigen Neugeborenen, dieser betrug 5,15 µg/ml. Dieser Wert war statistisch höher als der entsprechende der Gruppe der untergewichtigen Neugeborenen, dieser betrug 5,15 µg/ml (Abb. 5)
Ähnliche Werte wurden erhalten, wenn die mütterlichen Östriol-Spiegel gemäß dem Geburtsgewicht berücksichtigt wurden (Abb. 7). **Die Analyse der Oxytozinase-Werte ergaben keine statistisch bemerkenswerten Differenzen.**
Willkürlich festgelegte Grenzwerte waren für HCS und Östriol 7 µg/ml und 35 ng/ml. Wenn die Werte niedriger als diese Spiegel waren, war bei den Neugeborenen die Möglichkeit der Untergewichtigkeit größer (Abb. 6 und 8).
Der Aussagewert war der beste, wenn beide Hormone gleichzeitig berücksichtigt wurden (77%) (Abb. 9). Diese Ergebnisse zeigen die Eignung der HCS- und Östriol-Bestimmung zur Voraussage des fetalen Wachstums.

Schlüsselwörter: Fetales Wachstum, HCS, Neugeborenes, Östriol, Oxytozinase, Risikoschwangerschaften, Untergewichtigkeit.

Résumé

La somatomammotropine chorionique humaine, l'éstriol et l'oxytocinase comme indices de la croissance foetale
Un groupe de 56 femmes avec grossesse à haut risque ont fait l'objet d'examens à partir de la 32ème semaine de gestation. En vue d'obtenir des indicateurs sûrs de croissance foetale, nous avons déterminé les degrés de somatomammotropine chorionique humaine, d'estriol et d'oxytocinase du sérum maternel. Les deux premiers ont été mesurés par radioimmunoessais spécifiques et la troisième par méthode colorimétrique. **Les valeurs moyennes obtenues la semaine précédant à l'accouchement pour les deux hormones et l'enzyme ont été en corrélation avec le poids des nouveaux-nés. Les coefficients de corrélation ont été respectivement de 0,30, 0,33 et 0,30 pour la sch, l'estriol et l'oxytocinase (fig. 2, 3 et 4).**
Les nouveaux-nés ont été classés en deux groupes selon qu'ils avaient du souspoids ou un poids conforme pour l'âge gestationnel considéré. Le degré de SCh maternelle correspondant aux nouveaux-nés avec un poids de naissance normal pour leur âge gestationnel s'est chiffré à 7,94 μg/ml. Cette valeur a été statistiquement plus elevée que celle correspondant au groupe des nouveaux-nés immatures et qui n'a pas dépassé 5,15 μg/ml (fig. 5).
Des résultats similaires ont été obtenus pour les degrés d'estriol maternel selon les divers poids de naissance (fig. 7).
Par contre, la même analyse appliquée à l'oxytocinase n'a pas révélé de différences statistiquement significatives.
Des degrés critiques arbitraires ont été fixés respectivement pour la SCh et l'estriol à 7 μg/ml et 35 μg/ml. S'ils sont inférieurs à ces seuils, on observe une plus grande probabilité d'immaturité pour les nouveaux-nés (fig. 6 et 8). **Le pronostic est le plus précis en cas d'évaluation simultanée de ces deux hormones (77%) (fig. 9).** On peut donc recommander la mesure de la SCh et de l'estriol si on veut déterminer l'évolution de la croissance foetale.

Mots-clés: Croissance foetale, estriol du sérum, grossesses à haut risque, nouveaux-nés de poids normal, nouveaux-nés immatures, oxytocinase du sérum, SCh.

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Bibliography

[1] BABUNA, C., E. YENEN: Further studies on serum oxytocinase in pathologic pregnancy. Amer. J. Obstet. Gynec. 94 (1966) 868
[2] CAPURRO, H., S. KONICHEZKY, D. FONSECA, R. CALDEYRO-BARCIA: A simplified method for diagnosis of gestational age in the newborn. J. Pediat. 93 (1978) 120
[3] CURBELO, V.: Crecimiento intrauterino. Monografía, Escuela de Graduados. Facultad de Medicina, Montevideo, Uruguay, 1973
[4] CURZEN, P., R. VARMA: A comparison of serum cystine aminopeptidase and urinary estrogen excretion as placental function tests. Amer. J. Obstet. Gynec., 115 (1973) 929
[5] DICZFALUSY, E.: Steroid metabolism in the human foetoplacental unit. Acta Endocr. 61 (1969) 649
[6] FISCHER-RASMUSSEN, W.: Maternal plasma oestrogen levels in relation to birth weight and sex. Abstr. Acta Endocr. 73 (1973) 177
[7] FISCHER-RASMUSSEN, W.: Maternal plasma oestrogen levels in relation to birth weight and sex. Acta Obstet. Gynec. Scand. 53 (1974) 47
[8] GENAZZANI, A. R., F. COCOLA, P. NERI, P. FIORETTI: Human chorionic somatomammotropin (HCS) plasma levels in normal and pathological pregnancies and their correlation with the placental function. Acta Endocr. 71 (1972) 167
[9] GOEBELSMAN, U., H. KATAGIRI, F. Z. STANCZYK, C. CETRULO, R. K. FREEMAN: Estriol assays in obstetrics. J. Steroid. Biochem. 6 (1975) 703
[10] GORWILL, R. H., I. R. SARDA: Hormonal studies in pregnancy. II. Unconjugated estriol in maternal peripheral vein, and cord artery serum at delivery in pregnancies complicated by intrauterine growth retardation. Amer. J. Obstet. Gynec. 127 (1977) 17
[11] HENSLEIGH, P. A., K. E. KRANTZ: Oxytocinase and placental function. Amer. J. Obstet. Gynec., 107 (1970) 1233
[12] HURRY, D. J., J. E. TOVEY, D. A. ROBINSON, C. L. BEYNON, K. COOPER: Cystine aminopeptidase in normal and complicated pregnancies. J. Obstet. Gynaec. Brit. Cwlth., 79 (1972) 788
[13] JAMES, N. T.: Histochemical demonstration of oxytocinase in the human placenta. Nature 210 (1966) 1276
[14] JOSIMOVICH, J. B.: Placental protein hormones in pregnancy. Clin. Obstet. Gynec. 16 (1973) 46
[15] KUNZ, J., P. J. KELLER: Ultrasound and biochemical findings in intrauterine growth retardation. J. Perinat. Med., 4 (1976) 85
[16] LETCHWORTH, A. T., R. J. BOARDMAN, CH. BRISTOW, J. LANDON, T. CHARD: A rapid semi-automated method for the measurement of human chorionic somatomammotropin. The normal range in the third trimester and its relation to fetal weight. J. Obstet. Gynaec. Brit. Cwlth. 78 (1971) 542
[17] LINDBERG, B. S., B. A. NILSSON: Human placental lactogen (HPL) levels in abnormal pregnancies. J. Obstet. Gynaec. Brit. Cwlth. 80 (1973) 1046
[18] LINDBERG, B. S., E. D. S. JOHANSSON, B. A. NILSSON: Plasma levels of nonconjugated oestradiol-

17 B and oestriol in high risk pregnancies. Acta Obstet. Gynec. Scand. Suppl. 32 (1974) 37
[19] MASSON, G. M.: Plasma estriol in preeclampsia. J. Obstet. Gynaec. Brit. Cwlth. 80 (1973) 206
[20] PATHAK, S., A. HIMAYA, R. MOSHER: The small-for-dates syndrome: some biochemical considerations in prenatal diagnosis. Amer. J. Obstet. Gynec. 120 (1974) 32
[21] PETRUCCO, O. M., K. CELLIER, A. FISHTALL: Diagnosis of intrauterine fetal growth retardation by serial serum oxytocinase, urinary oestrogen and serum heat stable alkaline phosphate (HSAP) estimations in uncomplicated and hypertensive pregnancies. J. Obstet. Gynaec. Brit. Cwlth. 80 (1973) 499
[22] ROBINSON, H. P., W. R. CHATFIELD, R. W. LOGAN, A. K. TWEEDIE, W. P. BARNARD: A scoring system for the assessment of multiple methods of monitoring fetal growth. J. Obstet. Gynaec. Brit. Cwlth. 80 (1973) 230
[23] RYDEN, G.: Cystine aminopeptidase activity in pregnancy. Acta Obstet. Gynec. Scand., 50 (1971) 253
[24] SCIARRA, J., S. L. KAPLAN, M. M. GRUMBACH: Localization of anti-human growth hormone serum within the human placenta: Evidence for a human chorionic growth hormone-prolactin. Nature 199 (1963) 1005
[25] SHEARMAN, R. P., D. A. SHUTT, I. D. SMITH: The assessment and control of human fetal growth. In: Ciba Foundation Symposium. Size at birth. Associated Scientific Publishers, Amsterdam, 1974
[26] SPELLACY, W. N., W. C. BUHI, J. D. SCHRAM, S. A. BIRK, S. A. MACCREARY: Control of human chorionic somatomammotropin levels during pregnancy. Obstet. and Gynec., 37 (1971) 567
[27] SPELLACY, W. N., M. USATEGUI-GOMEZ, A. FERNANDEZ de CASTRO: Plasma human placental lactogen, oxytocinase and placental phosphatase in normal and toxemic pregnancies. Amer. J. Obstet. Gynec., 127 (1977) 10
[28] SPENCER, T. S.: Human chorionic somatomammotropin in the third trimester of pregnancy. J. Obstet. Gynaec. Brit. Cwlth. 78 (1971) 232
[29] TUPPY, H., H. NESVADBA: Mh. Chem. 88 (1957) 977
[30] WHITE, P.: Pregnancy and Diabetes. Medical Aspects. Med. Clin. N. Amer. 49 (1965) 1015

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