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SUMMARY

In the present report, cholestasis enzymes have been observed during pregnancy, with study made of the three most important enzymes of cholestasis in serum: alkaline phosphatase (PHA), leucine amine peptidase (LAP), γ-glutamil transpeptidase (γ-GT).

In accordance with previous data, alkaline phosphatase and leucine amine peptidase levels were found to increase during the 3rd trimester of pregnancy, remaining elevated during the first week of puerperium, while no increase was observed in γ-glutamil transpeptidase in patients during pregnancy. The above changes in serum concentration of enzyne activity were all statistically calculated.

This study of cholestasis enzymes indicates the present of high concentrations, of PHA and LAP placenta tissue, with an absence of γ-GT. On the basis of these results, it is suggested that value of γ-GT in serum is the only index of cholestasis liver during pregnancy.

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Our experience in Monitoring pregnancy and delivery

by

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The decrease of the perinatal mortality rate is conditioned by the possibility of an early diagnosis of states of acute and chronic fetal destress, which can manifest themselves during pregnancy or labor.

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It is well known that fetal death or destress are preceded by a series of pathological events which are usually diagnosed too late by common clinical means.

As a result, modern physical and biochemical diagnosis should be based on multiple methods. Because of the complexity of fetal maternal relations, none of these methods alone is capable of furnishing complete and reliable information.

Here we are reporting the results of our own clinical experience, emerging from the systematic application of some of these methods which were shown to be valid for that scope.

I During pregnancy they are: *a*) for the biophysical aspects: the weekly control of fetal dimensions, by ultrasonography, and of the fetal heart rate; *b*) for the biochemical aspects: a control every two days of urinary estriol, of placental lactogen and of alphafetoprotein in the plasma.

Only in selected cases, in which an evaluation is still in course, was the behavior of plasma HCG studied.

Table 1. *Semiology during pregnancy.*

BIOPHYSICAL METHODS	*BIOCHEMICAL METHODS*
1 - Biparietal diameter	1 - Plasma and urinary H.C.G.
2 - Ante-partum cardio-tocography	2 - Plasma placental lactogen
3 - Atropine-test	3 - Urinary estriol/creatinine ratio
	4 - Plasma alpha-feto protein

In regards to the effective validity of the single diagnostic methods used in the more frequent forms of pathology seen in pregnancy, our data seem to be quite significant. The most preoccupying aspects of these problems regards more so the false-negatives rather than the false-positives, even if the latter causes a certain amount of apprehension on part of both the patient and the physician, and sometimes even risk to cause prematurity that we can define as « iatrogenic ».

We should however take into account possible sources of experimental error for each method. For the ultrasound measurement of the biparietal diameter, it has been possible to determine the accuracy of this method.

As for the biochemical tests, it is fundamental to refer to a curve of normal values, which each laboratory should determine for itself, without making reference to data found in the literature which is frequently obtained under different experimental conditions.

At last you have to take into account the biological variations of the single parameters: where this is too big, you will see a superimposition of the normal and pathological values such that later on in clinical practice it will be very difficult to determine the borderline between physiological and pathological; in that case the diagnostic value will be uncertain.

Thus in relation to each gestational age, we have determined for every diagnostic method the mean values and standard deviations on the basis of results obtained by our laboratories in clinically normal pregnancies (mostly on the basis of their outcome), and we have considered as pathological values which differ by more than one standard deviation from the mean.

We have controlled, in retrospect, the validity of the single methods in a sample of patients affected by the principal forms of pathology clinically observed during pregnancy: premature labour, toxemia, fetoplacental insufficiency, diabetes, and Rh isoimmunization.

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Table 2. *Presenting features in the patients.*
(mean values)

	n. of cases	gestational age at delivery	birth weight	placental weigh
Premature delivery	17	30 weeks	1345 g.	316 g.
Toxemia	23	39 weeks	3370 g.	645 g.
Placental insufficiency	23	39 weeks	2445 g.	334 g.
Diabetes	3	35 weeks	3450 g.	670 g.
Rh. Isoimm.	6	38 weeks	3000 g.	970 g.

The results are the following: A) Biophysical diagnosis:

1) The *biparietal diameter* gives a fairly exact prevision of fetal weight, and so the diagnosis of deviations of intrauterine growth. It also serves however to monitor cerebral development of the fetus and to establish a prognosis for successive cerebral function. In our statistics, the biparietal diameter was normal in 40% of all premature births, greater than the norm in 20%, and less than the norm in the remaining 40%.

The high incidence of « small for date » fetus in premature births is due to the increased uterine contractility which precedes the delivery. This reduces the uterine-placental blood flow. In these cases, our clinical experience has confirmed the utility of tocolytic therapy with beta-mimetics, that, if begun early enough, can normalize the duration of the pregnancy in 90% of cases.

Table 3. *Biparietal Diameter (B.P.D.).*

	Low	Normal	High
Premature delivery	40%	40%	20%
Toxemia	6%	94%	0%
Placental insufficiency	35%	65%	0%
Diabetes	0%	78%	22%
Rh Isoimm.	0%	100%	0%

In toxemia, the biparietal diameter was reduced in 6% of the cases and most of all hypertension was the cause of placental vascular damage. In the acute forms, the damage does not necessarily have to produce a slowed intrauterine fetal growth.

In placental insufficiency the biparietal diameter was significantly less than the norm in 35% of the cases and it was never greater. There exists, a certain number of cases of placental insufficiency which are not accompained by a slowing of the intrauterine growth of the fetus. It can be concluded that the histopathological alterations in these cases, were not sufficient enough to reduce the nutritional exchanges.

On the other hand, there exist « small for date », whose scarse development is not related to placental insufficiency but to other causes, for example, genetic or toxic causes.

In diabetes, more or less controlled, the biparietal diameter was significantly greater than the norm in 22% of the cases, but never was it less.

In Rh isoimmunization the biparietal diameter was always normal.

2) *The Fetal heart rate*, recorded at least 30 minutes every week during the second half of pregnancy, permits us to show « beat to beat » variations.

Table 4. *Ante-Partum Cardio-Tocography (time period of registration required: 30 minutes).*

	AMPLITUDE OF BASIC F.H.R. (persistent over 10 minutes)				
	silent	narrowed	ondulatory	spontaneous saltatory	LATE decelerations
Normal pregnancy	–	–	+	–	–
Toxemia	+	–	–	+	+
Placental insufficiency	–	+	–	+	+
Diabetes	–	–	–	+	–

These always become more evident as the gestational age progresses, and are related to motor activity, to the awake or asleep states, to the cerebral reactivity, and also to the oxgenation of the fetus. Some drugs when administered to the mother (sympathomimetics, atropine barbiturates, diazepam, beta-blockers) can alter this finding. Variations of the instantaneous fetal heart rate can indicate, if accentuated enough, a state of fetal stress or when they are almost absent (silent rhythm) a state of placental insufficiency. From our experience, an ondulatory rhythm, considered normal, is never associated with fetal or placental pathology. On the contrary however, tracings which differ from the norm can be found in toxemia, placental insufficiency, diabeted, Rh isoimmunization, and umbilical cord pathology.

It should be noted that this method does have its limits, especially for the difficulties in classification of some tracings and in a certain number of false-negatives.

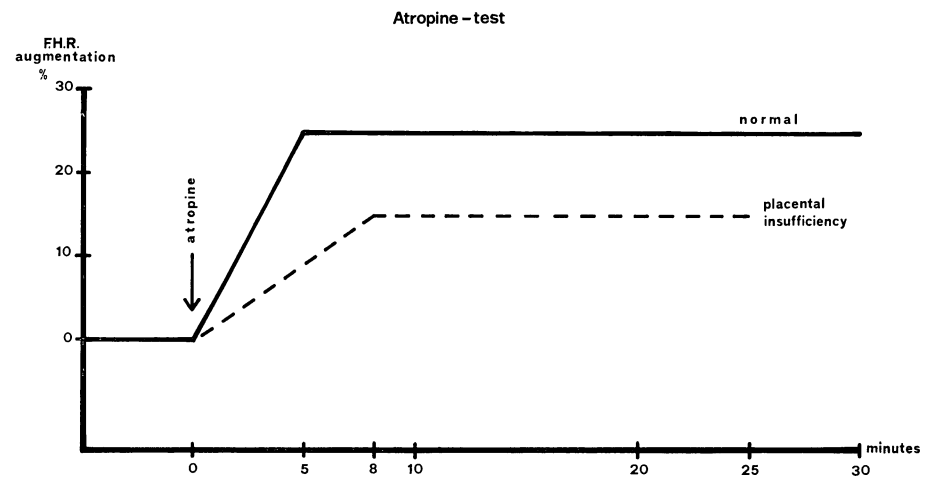

FIG. 1.

Intravenous administration of atropine to the subject (atropine test) during the third trimester permits the functional exploration of maternal-fetal exchange: the continuous recording of the heart rate permits us to evaluate the latency and the entity of fetal vagal inhibition.

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This test shows a characteristic behavior only when notable placental alterations are present and in single cases it does not always permit a definite diagnosis; thus from our experience it is less reliable than other diagnostic methods.

B) Biochemical diagnosis is based on the classical determination of urinary estriol, together with more recent methods of plasma radioimmunological dosing of placental lactogen and of alphafetoprotein; some enzymatic indices, such as heat-stable alkaline phosphatase and cystine-amino-peptidase, have been abandoned, because of the wide range of variability even under normal conditions and thus their scarse reliability.

1) *Urinary estriol* corrected on the basis of creatinine excretion (estriol/creatinine ratio) shows 7% false positive values or low values in normal pregnacies, and 10% false-negatives or normal values in pregnancies with fetal-placental pathology. However a normal estrioluria confirms an absence of fetal destress in 90% of all cases. In premature labour, the weekly average for the E/C ratio in always normal (56% of all cases) or high (44% of all cases). This tendency towards a high estrioluria in premature births has already been described in the literature.

Table 5. *Urinary Estriol/Creatinine ratio.*

	Low	Normal	High
Normal pregnancy	7%	93%	
Feto-placental pathology	90%	10%	
Premature delivery	0%	56%	44%
Toxemia	33%	58%	9%
Toxemia with low B.P.D.	80%	20%	0%
Placental insufficiency	50%	30%	20%
Placental insufficiency with low B.P.D.	70%	30%	0%
Diabetes	0%	3%	97%
Rh Isoimm.	100%	0%	0%

Analogous results were obtained for the estriol levels when tested in placental insufficiency: 50% pathological values and 70% in the presence of a reduced biparietal diameter.

In diabetes almost always (97%) the estrioluria appeared significantly elevated but it was always normal in severe erythroblastosis fetalis (pre-hydrops and hydrops).

Thus the estriol level is a useful index mostly in chronic fetal distress associated with deficient intrauterine growth.

Table 6. *Plasma placental lactogen.*

	Low	Normal	High
Normal pregnancy	17%	83%	
Feto-placental pathology	65%	35%	
Premature delivery	0%	50%	50%
Toxemia	74%	19%	8%
Placental insufficiency	58%	35%	7%
Placental insufficiency with low B.P.D.	100%	0%	0%
Diabetes			100%
Rh Isoimm.		100%	

2) The level of placental lactogen is a direct measure of the syncytial-trophoblastic mass: it gives 17% false-positive (low values in normal pregnancies) and 35% false negatives (normal values in pathological pregnancies).

In premature labour, HPL was never less than normal, but in half of the cases it was higher.

In toxemia, placental lactogen was low in 74% of the cases, and in placental insufficiency it was low in 58% of the cases, a percentage which increases to 100% if associated with reduced fetal development.

Normal or high HPL values can be found in diabetes with fetal macrosomia, and in severe Rh isoimmunization.

The determination of HPL levels was indicative mostly in global placental alterations.

3) We have systematically used the determination of plasma alphafetoprotein. This fetal parameter is not completely understood in all of its physiopathological aspects, however the results up until now are promising.

Table 7. *Plasma alpha-feto protein.*

	Low	Normal	High
Normal pregnancy	17%	83%	
Feto-placental pathology	82%	18%	
Premature delivery	30%	55%	15%
Toxemia	33%	59%	8%
Placental insufficiency	37%	44%	20%
Diabetes		100%	0%
Rh Isoimm.		0%	100%

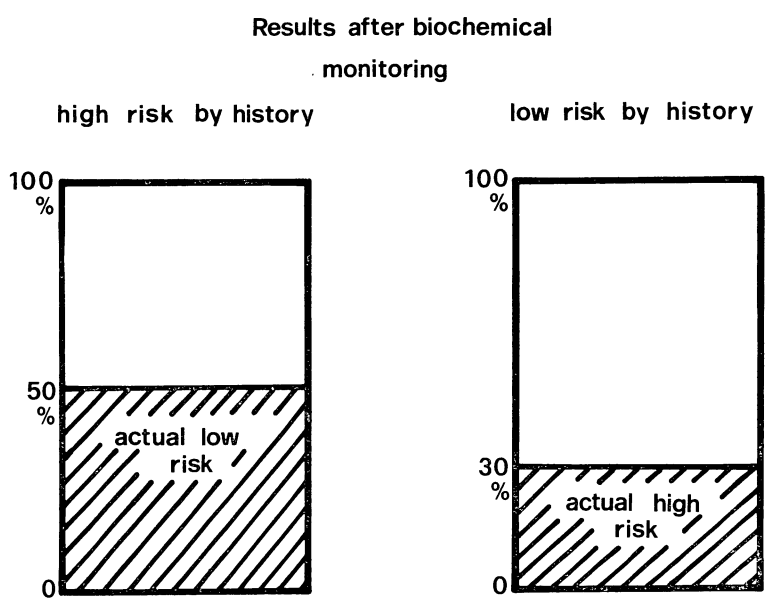

FIG. 2.

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The maternal plasma level should be in relation to fetal alpha-fetoprotein synthesis and therefore showes the quantity of the aminoacid pool available for proteo-synthesis: a dietary lack in fact alters the relationship RNA synthesis/ protein synthesis.

The following results, even if they still need further confirmation, are fairly indicative.

The determination of alpha-fetoprotein shows, on the average, 17% false-positive (low values in normal pregnancies) and 18% false-negatives (normal values in pathological pregnancies). In Premure labour alpha-fotoprotein is within the norm, as long as fetal development is not scarse (30% of cases). Analogous behavior is also seen in toxemia and in placental insufficiency (33% and 37% of values less than the norm respectively). In diabetes and Rh isoimmunization with normal fetal development, the plasma values of alpha-fetoprotein were normal, except in cases of imminent fetal death.

Thus we can see now the importance of the study of the correlation between plasma alpha-fetoproteins and the biparietal diameter. In conclusion we believe that the extensive application of these methods, for all pregnancies followed at the Out-Patient Clinic of Padua, has really provided us with the information necessary to define certain pregnancies as the « High-risk type ».

In fact the concept of risk based only on a history is totally insufficient and has to be corrected on the basis of the results of physical and laboratory tests. Research in that way, has shown that only 50% of pregnancies determined to be « High risk » by history were really high-risk, and that 30% of low risk pregnacies by history had objective elements that would classify them as high risk.

II During labour, fetal destress is usually a consequence of a pathology existing during the pregnancy, which can be diagnosed in large part by extensive monitoring, which does not take into account only high risk pregnacies. The same approach is also fundamental for the early diagnosis of acute fetal distress during labour. Therefore we feel that almost all fetal pathology can be diagnosed by just using continuous and extensive monitoring; *continuous* or for the entire duration of labor, because fetal conditions can vary greatly in proportion to its development; *extensive* because fetal distress is not forseen in low risk pregnacies.

Constant recourse to the partogram can facilitate many times evidencing dynamic dystocias in particular the excessive duration of the dilating period, a frequent cause of progressive fetal distress.

Table 8. *Semiology in labour.*

Intra-partum cardio-tocography	44,3%
Good quality of tracing (non invasive monitoring)	88,4%
False positives	9,8%
False negatives	5,5%
Biochemical monitoring (pH, pCO_2, B.E.)	3,7%

Basic monitoring can be represented by a cardiotocographic control of all patients, for which is needed adequate technical means and trained personnel.

At Padua we have not reached these conditions yet; for 2000 annual deliveries

we have monitored cardiotocographically 44.3% of the patients. There is actually 1 cardiotocograph available for every 400 deliveries per year.

The quality of the tracing, usually obtained by external monitoring, is qualitatively excellent in 88% of all cases, and in nearly 100% of all cases if you consider only internal monitoring.

Naturally the use of external monitoring permits us to control the whole duration of labor, even the begining of the dilatation period when with the first contractions there sometimes appears fetal distress from placental insufficiency.

Cardiotocography is not without error; in our statistics we had 9,8% false positives and 5,5% false negatives.

The false positives are eliminated by biochemical monitoring, which is done when indicated by electronic monitoring, on the average 3,7% of all cases.

More serious is the incidence of false-negative, due in some part to the bad quality of the tracings and for the rest due to the limits of cardiotocography.

Analysis of the results in terms of perinatal mortality however is very complex; you have to take into account that many patients are admitted only at the moment of delivery without an adequate monitoring of the pregnancy and thus the fetal mortality rate between the 28th week and delivery escapes any real possibility of control.

Even more difficult is the evaluation of perinatal morbility and most of all the outcome at some distance; for that reason there are in couse for those patients who were monitored during pregnancy and the delivery, evaluation of results up until 2 years.

In conclusion we feel that the monitoring of the pregnancy and delivery, even if it needs notable economic and technical assistance, and sometimes furnishes results constitutes an unrenounceable method in the field of modern obstetrical assistance.

Radial immunodiffusion: a new method for the evaluation in the serum of the placental lactogenic hormone

by

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The term placental lactogenic hormone (HPL or HCS) was coined in 1962 by Josimovich *et al.* (1) Subsequent studies have demonstrated that this hormone is synthetized and secreted by the cells of the placental trophoblastic syncytium (2). Spellacy *et al.* (3), had already recognized, in 1967, that analysis of HPL carried out on the serum of a pregnant woman could be used as a functional placental test throughout pregnancy. Many opinions to-day confirm that this can be done, although there may be some risk in certain circumstances due to functional in-

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