WHAT ARE THE MOST SUITABLE FETOPLACENTAL TESTS IN THE MONITORING OF THE THIRD TRIMESTER OF PREGNANCY?

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SUMMARY

The case-series of the Institute of Obstetrics and Gynaecology were examined to evaluate the suitability of urinary estriol, total plasma estriol, unconjugated plasma estriol, unconjugated plasma estetrol, plasma placental lactogen, plasma S.P.-1 glycoprotein, plasma alphafetoprotein and biparietal diameter in correctly forecasting the perinatal risk, when performed after the 25th week of pregnancy.

In high-risk pregnancies, according to our results, S.P.-1 glycoprotein and urinary estriol are the most sensitive tests, while S.P.-1 glycoprotein, placental lactogen and biparietal diameter are found to have the highest predictive value.

The repetition of the considered tests increases their sensitivity, but not their predictive value.

In pregnancy mass screening the most suitable tests, on the basis of the "relative risk" are S.P.-1 glycoprotein (or even placental lactogen), estriol and biparietal diameter. For the last one a single measurement seems to be enough during the third trimester.

In order to better control the fetal wellbeing, the traditional obstetric visit has been supported in the last years by several biochemical and biophysical investigations, which are widely used in the University but also in peripheral Hospitals ([1]). Many physicians, however, still question the real usefulness of these new pregnancy tests, for want of evidence of a favourable ratio between their costs and benefits.

Many studies describe the diagnostic reliability of the single tests in pregnancy complications and report their "true-positive" and "false-negative" incidence, without yet evaluating their corresponding "false-positive" and "true-negative" incidence in a proper group of normal pregnancies. Even harder problem seems the lack of definition of the range of normal values, by means of proper statistical criteria ([2]).

The lack of these requisites makes many studies unsuitable for the purpose of solving the problem we are discussing.

On the other hand, a different approach is needed if the pregnancy monitoring is to be applied outside hospitals: most pregnant women are quite healthy and they need of a correct monitoring which can effectively predict the pregnancy outcome, while diagnostic tests for specific diseases can't be considered justified at all.

The aim of this work is to evaluate, by the use of proper methods and statistical descriptors, the ability of the single tests to provide not only exact diagnoses, but also previsions on the pregnancy outcome in terms of overall perinatal risk, that is to determine the actual obstetrical risk.

MATERIAL AND METHODS

The case-series consists of single pregnancies longitudinally monitored since the 25th week of gestation until term.

On the basis of perinatal outcome, this sample was divided into two groups and the following characteristics were present in the "normal" group:

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— certain pregnancy-lenght of 38-40 weeks,
— birth weight between the 10th and 90th centile, according to sex and gestational age,
— Apgar score higher than 7 at the 1st minute,
— lack of major congenital malformations and of any remarkable morbidity in the postnatal period.

The cases which failed to meet even one of these requirements were considered to have a pathological perinatal outcome.

As not all the tests were performed in each pregnant woman, their distribution in the two groups of perinatal risk is showed in the table 1.

The determination methods were already described elsewhere ([3]).

Statistical analysis

The confidence limits of the normal range were calculated on the data from the cases presenting normal perinatal outcome by the use of a non-parametric method in order to avoid arbitrary assumptions on the distribution. The number of data was never lower than 50 per gestational week. The centiles were submitted to a polynomial approximation, in order to obtain a regular curve fitting without any arbitrary interpolation.

Values below the 10th centile were considered abnormal for all tests but alphafetoprotein, for which also the values above the 90th centile were considered abnormal.

The values were thus classified and compared with the corresponding perinatal outcomes to find the number of false positives, false negatives, true positives and true negatives.

On the basis of these elements, each test was evaluated from the point of view of sensitivity, specificity and predictive value.

A part of cases could be followed through seriate determinations; the number of determinations varied from 4 to 20 for every patient.

Table 1. — *Case-distribution.*

Test	Perinatal outcome		% Pathologic outcome
	Normal	Pathologic	
Urinary estriol/creatinine ratio	920	568	38.17
Total plasma estriol	785	458	36.84
Unconjugated plasma estriol	578	197	25.42
Unconjugated plasma estetrol	357	171	32.38
Placental lactogen	1021	663	39.37
S.P.-1 glycoprotein	333	219	39.72
Alphafetoprotein	629	417	39.86
Biparietal diameter	555	335	37.64

Table 2. — *Cryterion for inclusion into the abnormal group on the basis of seriate determinations.*

No. of assays	Minimum required number of values below the 10th centile	Minimum required percentage of values below the 10th centile
4	2/4	50%
5	2/5	40%
6	2/6	33%
7	3/7	43%
8	3/8	37%
9	3/9	30%
10	3/10	33%
11	3/11	27%
12	3/12	25%
13	4/13	30%
14	4/14	28%
15	4/15	26%
16	4/16	25%
17	4/17	23%
18	4/18	22%
19	4/19	21%
20	4/20	20%

These patients were divided into two groups, on the basis of the trend of the seriate determinations: " normal result " group (all the values between the 10th and the 90th centile); " abnormal result" group (values fluctuating above and below the 10th centile or constantly below the 10th centile). To achieve an uniformity of classification, we required a threshold percentage of values below the 10th centile for the inclusion of cases into the second group; this percentage varied with the number of determinations, as illustrated in the table 2.

According to this classification of cases, we considered the perinatal outcome, the number of false positives, false negatives, true positives and true negatives and assessed the sensitivity, specificity and predictive value of each test.

RESULTS

The suitability of the single tests in providing a correct characterization of the overall perinatal risk is showed in the table 3.

The comparative evaluation of the ability of the different tests to detect the high-risk pregnancies among all pregnan-

Table 3. — *Suitability of the single tests in providing correct previsions of the overall perinatal risk.*

	Sensitivity %	Predictive value %	Specificity %
Estriol/creatinine ratio	41.19	56.79	80.65
Total plasma estriol	22.70	52.52	88.02
Unconjugated plasma estriol	20.81	36.94	87.89
Unconjugated plasma estetrol	13.45	31.08	85.71
Plasma placental lactogen	24.58	65.46	91.57
Plasma S.P.-1 Glycoprotein	50.00	69.93	87.78
Plasma alphafetoprotein	35.49	56.06	81.55
Biparietal diameter	25.07	68.85	93.15

cies con be made by calculating the "relative risk", that is the ratio between the percentage of positives confirmed as such and the percentage of negatives confirmed as such. The higher is the relative risk, the more suitable is the test in detecting the perinatal risk. The tests can be graded as follows, on the basis of the relative risk:

S.P.-1 glycoprotein = 2.97; biparietal diameter = 2.10; estriol/creatinine ratio = 1.88; placental lactogen = 1.87; alphafetoprotein = 1.63; unconjugated estriol = 1.61; total estriol = 1.55; unconjugated estetrol = 0.95.

The suitability of the tests, when they are seriately repeated, in providing a correct characterization of overall perinatal risk is showed in the table 4.

The "relative risk" of each test, when performed in single or seriate determinations, is showed in the table 5. The table shows that, for some tests, seriate determinations increase the ability to forecast the perinatal outcome.

Therefore, in all pregnancies, S.P.-1 glycoprotein, placental lactogen and estriol assays should be repeated several times because their relative risk is thus increased, while the biparietal diameter and alphafetoprotein repetition would be useless.

DISCUSSION

The method followed by this study enables us to answer two questions simultaneously: how useful are the various tests in high-risk pregnancies? How useful are they in the mass-screening of all pregnancies, regardless of the obstetric risk?

The answer to the first question is given by the simultaneous evaluation of the sensitivity and predictive value.

It must be remembered that the tests were not evaluated according to the presence of a particular pregnancy pathology, but to quantify the overall perinatal risk, i.e. the birth of high-risk neonate, which

Table 4. — *Suitability of tests in providing correct previsions of the overall perinatal risk when they are performed seriately.*

	Sensitivity %	Predictive value %	Specificity %
Estriol/creatinine ratio	56.71	58.46	76.92
Total plasma estriol	24.48	50.00	87.50
Unconjugated plasma estriol	20.83	29.41	79.66
Unconjugated plasma estetrol	20.00	36.36	84.44
Plasma placental lactogen	35.44	68.29	91.27
Plasma S.P.-1 Glycoprotein	64.00	76.19	89.58
Plasma alphafetoprotein	43.75	48.83	73.80
Biparietal diameter	32.14	66.66	89.65

Table 5. — *Comparison of the relative risk resulting from single and seriate determinations.*

	Single	Seriate
S.P.-1 Glycoprotein	2.97	4.40
Placental lactogen	1.87	2.50
Estriol/creatinine ratio	1.88	2.40
Biparietal diameter	2.10	2.03
Total plasma estriol	1.55	1.90
Alphafetoprotein	1.63	1.61
Plasma estetrol	0.95	1.22
Unconjugated plasma estriol	1.61	1.00

may have many causes, also concerning the mother.

According to these criteria, of course, no test can be expected to show an acceptable sensitivity and predictive value.

Nevertheless, some tests show better results in detecting high-risk pregnancies.

S.P.-1 glycoprotein and urinary estriol/creatinine ratio appear to be the most sensitive tests (tab. 3). Moreover, they are fairly cheap, they neither require sophisticated equipments nor observation of radioprotection rules, and can be easily performed in any hospital laboratory. The cost/benefit ratio is therefore very favourable. These methods detect 50% of the cases of perinatal risk.

The radioimmunoassay of estrogens, placental lactogen, alphafetoprotein and the echographic measurement of biparietal diameter were showed, on the contrary, to be much less sensitive.

To establish previsions on the pregnancy outcome is very important in high-risk patients and we must know to what extent the clinical management can rely on the results of the considered tests.

S.P.-1 glycoprotein, placental lactogen and biparietal diameter have shown the highest predictive value (67-70%); the percentage decreases to about 50% in the case of total plasma or urinary estriol and plasma alphafetoprotein.

To better characterize high-risk pregnancies, seriate determinations of the parameters of fetal wellbeing are often performed.

The results definitely show an increase in sensitivity, passing from 50% to 64% for estriol/creatinine ratio, from 24% to 35% for placental lactogen, from 25% to 32% for the biparietal diameter and from 35% to 43% for the alphafetoprotein. Conversely, no significant increase occurs for plasma estrogens.

On the contrary, seriate determinations do not improve the predictive value of various tests.

The second question regards the most suitable tests for the mass screening. Table 5 reports the results obtained by the application of a specific statistical descriptor, the "relative risk".

The most suitable tests are the two placental proteins (S.P.-1 glycoprotein and placental lactogen), estriol and biparietal diameter.

The effectiveness of the S.P.-1 glycoprotein should be remarked also in mass monitoring, due to its relatively low cost, easy feasibility and high relative risk: the cost/benefit ratio is definitely very favourable.

The measurement of biparietal diameter ranks second in this classification: it detects the most severe fetal growth deficiencies which are responsible for an important share of postnatal risk. Although this test is expensive, a single measurement in the last 15 gestational weeks is enough to screen the cases at risk, while the repetition does not increase the relative risk.

Estriol comes third as good mass screening monitoring method; it can be assayed either by the fluorimetric or by the radioimmunologic method, in urine or in plasma respectively. The former is less expensive.

A final answer about the mass screening comes from the comparison of the two series of figures in table 5: it shows that placental proteins and estriol should be repeatedly assayed owing to the increase in their relative risk. All the other tests should be repeated only for a close control of the high-risk pregnancies.

The results suggest the following conclusions: during the third pregnancy trimester every pregnant woman should undergo seriate assays of S.P.-1 glycoprotein or placental lactogen, estriol and a single measurement of biparietal diameter. High-risk pregnant women should undergo seriate assays of placental proteins, estriol and alphafetoprotein together with seriate

measurements of at least three fetal dimensions (biparietal diameter, thorax diameter and femoral lenght) ([4]).

BIBLIOGRAPHY

1) Grella P., Chizzolini M.: *Ginecologia Clinica*, *2*, 1, 1981.
2) Chard T.: *Normality and Abnormality*. In: "Plasma Hormone Assay in Evaluation of Fetal Wellbeing", edited by A. Klopper - Churchill Livingstone, Edinburgh, London and New York, 1976, page 1.
3) Onnis A., Grella P.: *Atti Soc. Ital. Ostet. Ginec.*, *59*, 17, 1978.
4) Grella P., Nardelli G. B., Resta P.: *J. Foetal Med.* (in press).