Long-term Study on the Statistical Properties of Uterine and Umbilical Arterial Resistance Indexes by Simple Doppler Velocimetry in Patients with Perinatal Prognosis Stratification: Part I

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Este trabajo esta dedicado a mis hijos Laura Lidia y José Mauricio, quienes piensan, con gran acierto, que la fisiología no existe, ya que todo es biología.
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Abstract. *The simple Doppler velocimetry is a non-invasive morpho-functional technique with great impact as a diagnostic auxiliary means in Perinatal Medicine, and has lead to the adoption of many functional indexes.*
A question which remains to be answered is: what is the probable interaction between uterine and umbilical arterial resistance indexes during fetal life? The answer will explain the effect of risk factors and/or final changes induced by etiopathogenic agents. The hypothesis of the present approach is that the statistical variability of such indexes is directly related to the biological strategy to achieve cardiovascular adaptation during the perinatal lapse. Hence, the goal of this study is to analyze the statistical variability for both uterine and umbilical arterial resistance indexes, from long-term observations in three patients with very different perinatal prognoses but sharing the common final condition of a live newborn child. This report tests the adjustment for the Gaussian distribution and the lineal regression for the data of the simple Doppler velocimetry.

Introduction

Simple Doppler velocimetry is a non-invasive morpho-functional technique with great impact as a diagnostic auxiliary means in Perinatal Medicine, and has lead to the adoption of many functional indexes [1, 2, 3].

Some studies have used the so called resistance arterial index (Resulting from the division of the maximum peak, related with systole, by the minimum level related with diastole). Such index in uterine vessels has been associated with a favorable gestational evolution, while the umbilical index resistance has been considered an indicator of fetal development [4, 5, 6, 7].

A question remaining to be answered is to define what is the probable interaction between uterine and umbilical arterial resistance indexes during fetal life. The answer will explain the effect of risk factors and/or' final changes induced by etiopathogenic agents.

The goal of this study is to analyze the statistical variability for both uterine and umbilical resistance indexes, from long-term observations in three patients with very different perinatal prognosis but with the common final condition of a live newborn. This report tests the adjustment for the Gaussian distribution and the lineal regression for the data of the simple Doppler velocimetry.

I. Observational Design, Patients and Method

The patients recruited for this study were attended at the integrated medical care program in the Gynecology-Obstetrics Divi-

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TABLE 1

Clinical Information on the Three Selected Patients in the Long-term Observation of the Uterine and the Umbilical Resistance Indexes.

	Initial State	Gestation Evolution	Late Perinatal Result
A	Non-risk clinical antecedents: 22-year-old woman, 1st gestation	Clinically Healthy	Clinically healthy mother and newborn (50 cm tall, 3.5 Kg, Apgar 9-10).
B	Repeated abortion antecedents: 28-year-old woman, Fifth gestation, 4 spontaneous abortions	Clinically Healthy	Clinically healthy mother and newborn (48 cm tall, 2.8 Kg, Apgar 7-8).
C	Rh-isoimmunization disease: 47-year-old woman, fourth gestation, 2 childbirth, one spontaneous abortion	Fetal Hemolisis: intraperitoneal trans-abdominal blood transfusion in 35:5 weeks.	Cesarean programmed at 39 weeks. Live newborn (53 cm tall, 4.0 kg, Apgar 7-9). Icteric disease of the newborn. Phototherapy without neurological sequelae at 4 weeks after birth.

sion service at the Hospital General de Cuautitlán-ISSEM. The clinical protocol was approved by the Ethical and Research Committee conforming with international procedures for Human investigation, included were the informed consents by the couples.

From fifteen final patients, three patients were selected based on different clinical evolutions. Table 1 shows the clinical information for the three clinical prognosis conditions.

1. Initial State, Perinatal Evolution and Late Perinatal Results [8]

The initial condition is determined by the presence or absence of a disease. In case a disease was present, its current clinical state was described, that is, its clinical classification, treatment, complications and/or sequelae. If a disease was not present the description consisted of hereditary-family antecedents, pathological and non-pathological antecedents, and gynecological data that established the actual patient's risk factors.

The risk conditions were defined as follows:

a) Patient with a clinically healthy perinatal condition without risk factors identified.

b) Patient with clinically healthy perinatal condition with previous repeated-abortion antecedents

c) Patient with a Rh-isoimmunization disease in her current second gestation.

These patients were observed throughout the perinatal evolution up to 4 weeks after delivery (see table 1).

The standard medical treatment for these clinically healthy patients included: monthly appointments, laboratory tests and ultrasonography imaging. The ultrasonographic studies discarded intrauterine retarded fetal growth alterations, macroscopic congenital malformations, identified placental location and maturation, and allowed for qualitative appreciation of the amniotic fluid (see figure 1).

According to the weight gain and gestational age for each patient, nutritional indications were given. For the isoimmunized patient, the treatment was given at a tertiary level care hospital [9].

II. Equipment, Measurement Technique and Registration Procedure

Simple Doppler velocimetry was obtained with commercial equipment using a 4-MHz transducer that had an automatic calibration sequence and an energy-dissipation potency within accepted values for use in humans. During the registration the display monitor permitted identification and recording of measurements of the characteristic wave forms of the uterine and umbilical arteries, giving the index resistance values for the events previously selected using the calipers.

In each session, resistance indexes for a time series of

FIGURE 1. Schedule of Medical Care and Procedures of Registration for the Study Patients.

Procedures / Weeks	Prenatal 16-18	24-26	30	34-36	38		2	4
Medical attention	•	•	•	•	•	B	•	•
Laboratory tests:						I		
Blood type	•							
Pap smear	•					R	•	
Blood glucose, urea and creatine	•						•	
Urinalysis	•					T	•	
Ultrasonographic studies	•	•		•		H		
Cardiotocographic test				•				
Placental macroscopic examinations						•		

ten consecutive waveforms for the left uterine artery (R_L), the right uterine artery (R_R), and the umbilical cord (R_F) were measured.

The measurements were carried out on a conventional exploratory table, with the back of its seat at an angle of 30 degrees; and the exploration zones (hypogastric and inguinal areas) were previously cleaned. When the patients were recruited, the sessions were performed the same day of every other week, at the same hour and by the same researcher until the end of gestation. The results of this study were analyzed later and did not influence the clinical management of the patients.

The current clinically healthy perinatal condition was established if none of clinical procedures (described in the figure 1), was capable of identifying some pathological conditions during the whole period of observation.

III. Results

1. Statistical Estimations

Adjustment to Gaussian Distribution

Each arterial resistance index value for the corresponding patient was tested against the Gaussian distribution mean using the non-parametric Kolgomorov-Smirnov test [10]. All the resistance index values except for the right uterine resistance index in patients A and C, had a spatial distance that suggests a low probability of concern for this distribution. See graphs 1a, 1b, 1c.

Linear Regression

Assuming the presence of homogeneity in variance, the interception, the slope and the regression coefficient were computed in relation to the time of gestation. The x-axis represents the time of gestation and the y-axis shows the value of the resistance index for each registration session. Each central point is an average of ten consecutive measurements with ± 2 standard deviations.

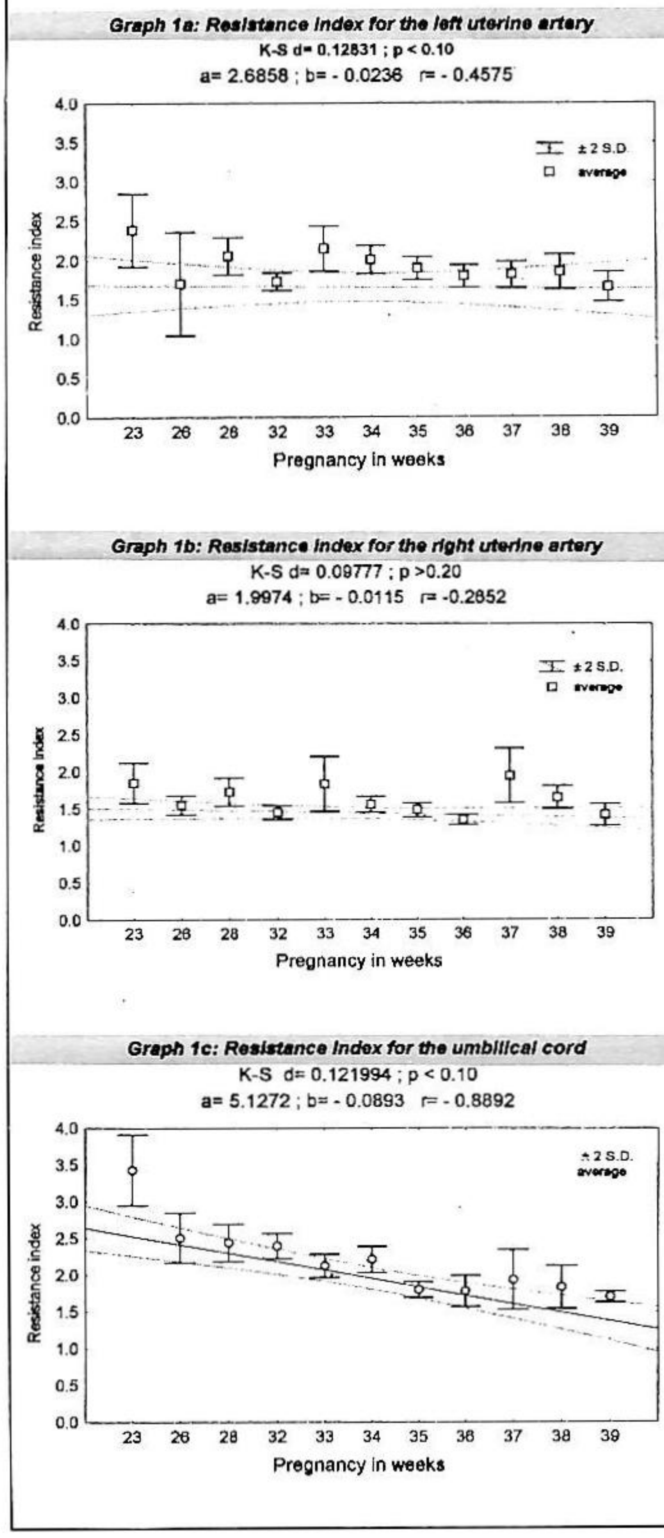
Patient A

Each 1a, 1b and 1c graphs represent 110 measurements performed on the corresponding vessel, giving a total number of measurements for all three graphs equal to 330. Note the negative value for all the slopes. The value of the regression coefficient is high for the umbilical index, moderate for the left uterine artery and low for the right uterine artery.

Patient B

2a, 2b, 2c graphs show 140 measurements on the corresponding vessel, for a total of 420 measurements. The slope was negative for all vessels. For both uterine arteries, the value for the coefficient of regression is moderate; on the other hand, the value for the umbilical cord was negative and lower in magnitude.

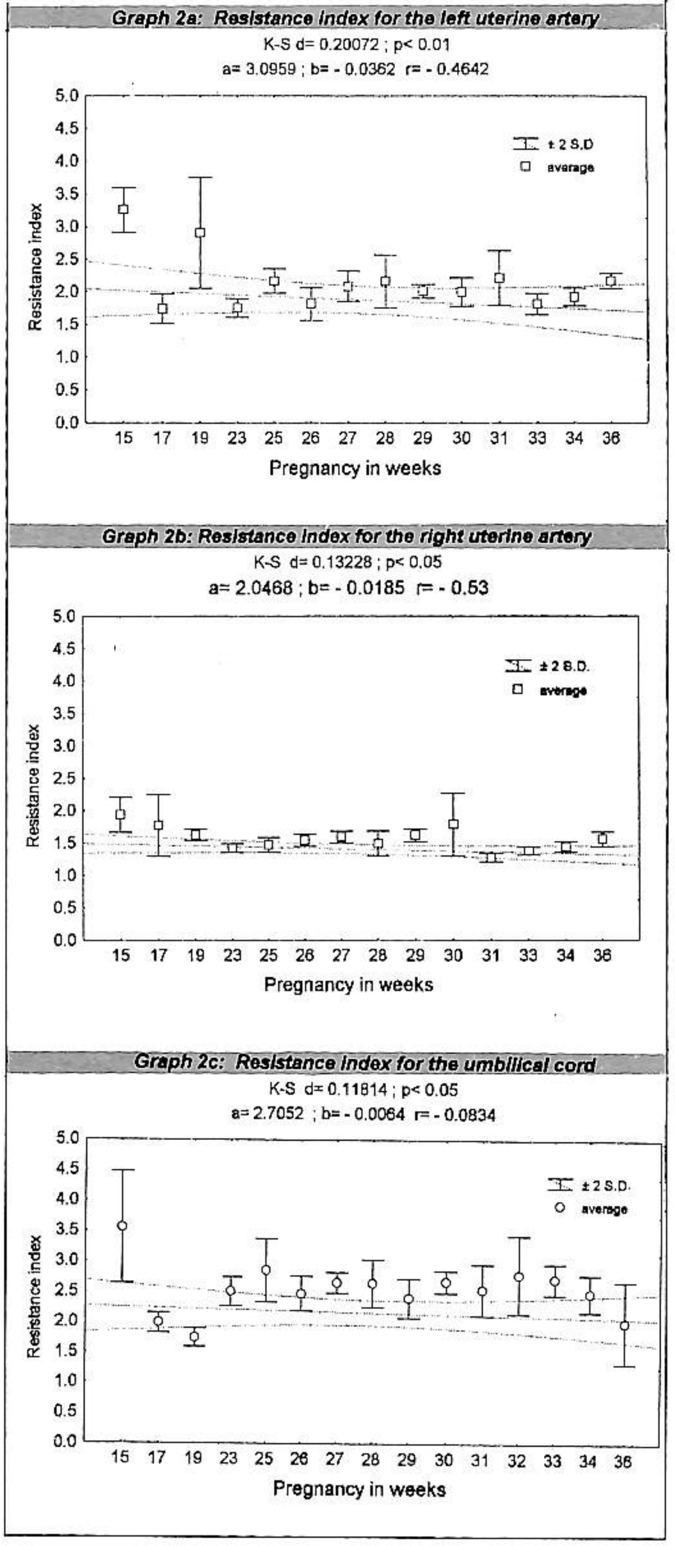
GRAPH 1. SIMPLE DOPPLER VELOCIMETRY PATIENT A. SPATIAL DISTANCE FROM GAUSSIAN DISTRIBUTION ADJUSTMENT FOR LINEAL REGRESSION.



Patient C

In this case, the 3a, 3b and 3c graphs permit one to see the values of 90 measurements obtained from the corresponding vessels, totaling 270 measurements. The slope was negative in the right uterine artery and in the umbilical cord, while positive in the left uterine artery. The

GRAPH 2. SIMPLE DOPPLER VELOCIMETRY PATIENT B. SPATIAL DISTANCE FROM GAUSSIAN DISTRIBUTION ADJUSTMENT FOR LINEAL REGRESSION.



regression coefficient for both uterine arteries was similar in magnitude but had opposing signs, while the umbilical cord value appeared high and positive.

For comparative purposes, graphs 4 and 5 show the behavior of the slope and the coefficient of regression for the resistance indexes. These graphs also contain the results obtained from the random data generated by a software program.

IV. Discussion

The magnitudes of the resistance index for the uterine arteries and the umbilical cord have been reported previously in transversal-study observations, where only two or three measurements were done in each patient to calculate a non representative average of resistance index [5, 6].

Moreover in such studies, there is no available information for a long-term observation in which the following factors have been accounted for: risk-antecedents, the entire gestation period and the late postpartum period (4 weeks). These characteristics may be important because the true clinical evolution can be hidden by the transversal type observation and deficient procedures of calculation.

In this concern, the present report establishes a great contrast, due to each vessel had been measured ten times to account for the true representative values of resistance. Also each patient is observed one other week for a careful monitoring session and specific program for medical management, to determine the status of health or disease, objectively.

The more ambitious goal of this longitudinal study is to see if the statistical variability for the three different initial conditions –with a common current healthy evolution–, reflects a particular strategy to cope with the biological challenge represented by the pregnancy. On three patients that exhibited a gradual perinatal risk were selected, as was defined previously.

Such statistical variability is expressed by the results obtained up to this part of the report and can be summarized as:

1. The probability of conforming to a Gaussian distribution for the data collected had a rank of $0.20 < p < 0.01$ when a non-parametric test was used.

Also many other probability distributions were tested unsuccessfully. There are many consequences from this finding. From a technical point of view this result implies that a non parametric statistical approach should be used for hypothesis contrasting. In another hand, others authors have emphasized the use of derived variables like this quotient carries many inconvenient due to many reasons, such as its relative inaccuracy, also does not provide information about the relationship between the two variables and its distributions may become atypical or non Gaussian [12] like the data in this study.

2. The data for all the patients has heterogeneity in variance. This can be seen by the amplitude in the bars that represent the standard deviation.

The data of the umbilical cord resistance may suggest an increased dispersion for both the initial and the final weeks of gestation and it appears to acquire a minimal value of dispersion in the central part of the observations (Check in the graphs, the non-continual lines of the 95% confidence interval). The variance of the uterine artery resistance indexes became more stable and had the lowest value when the uterine artery resistance índex was almost 1.5 (See graphs 1b, 2b and 3b).

Why this pattern of changes for the variance? There is no direct support for a simple answer, but it can be speculated an initial period of instability during the early organogenesic state. In the midterm of gestation can be thinking that an appropriate cardiovascular balance between fetus and mother have been established and thus the stability in variance. The final increased variance could be related with the onset of the imminent labor.

3. The values in the coefficient of linear regression were significant and the slope was negative only for the umbilical cord resistance index.

This result is very important, because the decreasing slope of the arterial resistance led to increased rates of blood perfusion to the fetus and thus to favorable course of the gestation.

On respect to the high interception value in patient C seems to be related with the concomitant pathology, and the negative slope probably reveals a very forceful homeostatic compensation. Patient B remains an open question, with its low coefficient value and negative slope, which may be due to the repeated abortions whereof etiology was not identified.

1. Limitations of the Statistical Model

The appropriate use of a linear model approach is based on the basic assumptions of randomness, independence and normality [11, 12]. Clearly the present data does not respond to such requirements, however, it permits one to recognize the characteristic of variability of the data and to establish a more adequate means for its solution.

2. Justification of the Statistical Study

The common practice based on "robust assumption" e.g. –The major part of the biological data pertains to Gaussian distribution–, has been misunderstood. Thereby it has been propitiated the indiscriminate application of parametric techniques without testing the statistical properties of the data. In such case can lead to invalidation of the inferential processing.

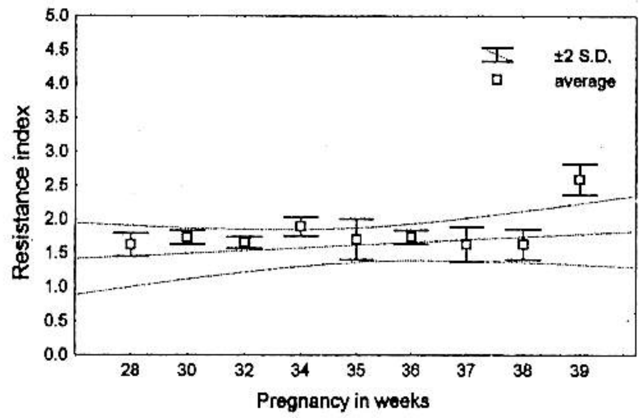
A previous statistical examination is obligated for every applied study, to accomplish the requirements of the linear approach. As a consequence the crucial selection between parametric and non parametric methods can be achieved.

GRAPH 3. SIMPLE DOPPLER VELOCIMETRY PATIENT C. SPATIAL DISTANCE FROM GAUSSIAN DISTRIBUTION ADJUSTMENT FOR LINEAL REGRESSION.

Graph 3a Resistance Index for the left uterine artery

K-S d= 0.25954 ; p< 0.01

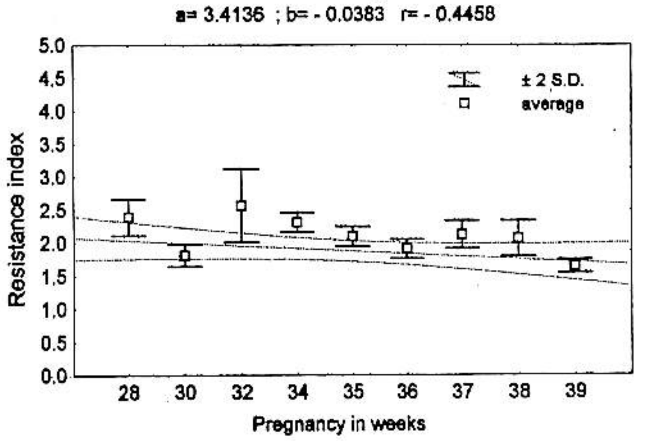
a= 0.50785 ; b= 0.03760 r= 0.43172



Graphic 3b: Resistance Index for the right uterine artery

K-S d= 0.07159 ; p> 0.20

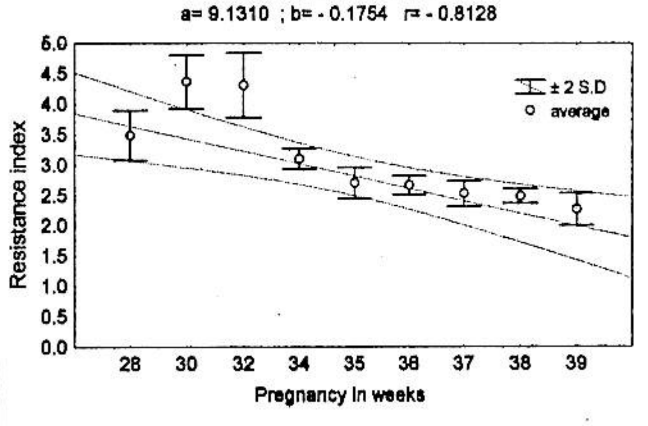
a= 3.4136 ; b= - 0.0383 r= - 0.4458



Graph 3c: Resistance Index for the umbilical cord

K-S d= 0.20639 p< 0.01

a= 9.1310 ; b= - 0.1754 r= - 0.8128

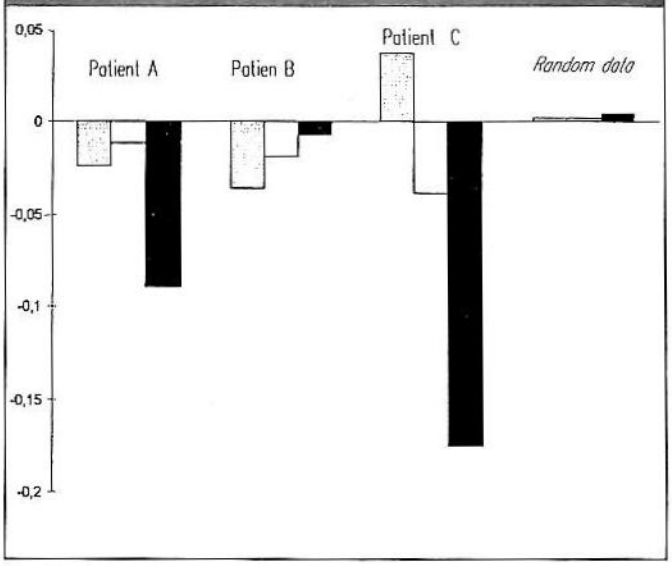


Conclusions and Perspectives

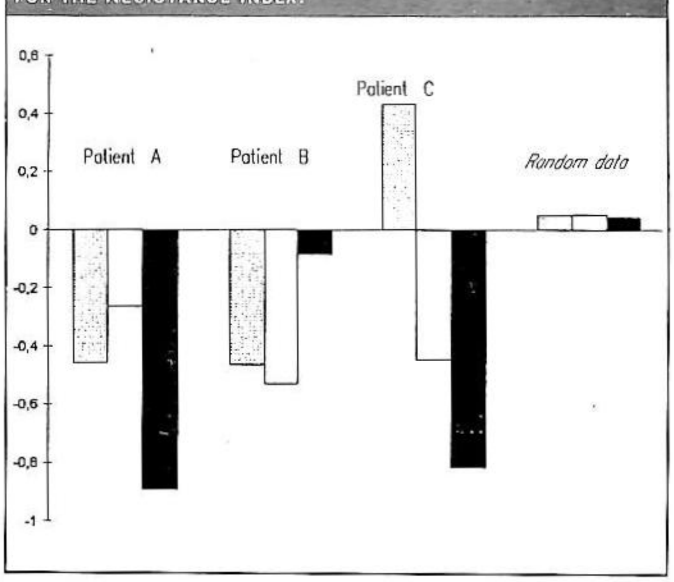
This first part of the report makes clear the complex array of physiological mechanisms presents in the three diverse states of the healthy patients through a longitudinal observation of the resistance indexes.

The specific contributions of this half are: a) The statistical variability of the data consists on a variable adjustment to a Gaussian distribution; b) Three very dif-

GRAPH 4. SLOPE MAGNITUDE VALUES FOR THE LINEAL REGRESSION OF THE RESISTANCE INDEX.



GRAPH 5. COEFFICIENT VALUES IN THE LINEAL REGRESSION FOR THE RESISTANCE INDEX.



ferent biological strategies may be related with the decreasing value of the slope for umbilical resistance index; c) The consequence of characteristics of randomness and normality of the data justify the ulterior application of non-parametric methods; d) There is heterogeneity of the variance that it can be related with fetal maturation stages; e) While the resistance for the uterine arteries appears to acquire a steady state value around 1.5, the umbilical cord resistance index has the highest regression coefficient value as well as a negative slope. These preceding changes may assure the viability of the fetus.

This global study can be considered a methodological assay, and this part explores the statistical variability utilizing a parametric approach, showing the obstacles and looking for the maximal benefices to acquire the crucial information accessible at this level.

In the second complementary part, linear correlation is used to complete the statistical properties of the data. At continuation, non parametric methods are used to overcome the special difficult giving for the statistical nature of data. Finally, it will be presented a new way of compute the total uterine arteries and an entire revision of the data.

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