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 II

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Abstract. Simple Doppler velocimetry is a non-invasive morpho-functional technique with great impact as a diagnostic auxiliary means in Perinatal Medicine, that has led to the adoption of many functional indexes.
One remaining question to be answered is to define which 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 this approach consists of that the statistical variability of such indexes is related with the biological strategy to achieve cardiovascular adaptation during the perinatal period.
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 prognosis but with common final condition of a live newborn.
In this report a new way of compute the total arterial uterine resistance index is presented, and how the Friedman-Anova rank test is utilized to search the probable statistical difference for the corresponding arterial resistance indexes among patients. Also, the nonlinear regression by exponential growth adjustment is used to describe the statistical variability of patients' data.
The total results obtained in this project support the beneficial approach of a long-term observational study and reveal a characteristic profile followed by three patients with very different perinatal prognosis as seen by the variability of statistical properties.

Introduction

Some studies have utilized 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 gestation evolution, while the umbilical index resistance has been considered an indicator of fetal development [1, 2, 3].

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

In the first part of this study, the adjustment of data for Gaussian distribution and linear regression coefficients were estimated for both

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uterine and umbilical resistance indexes. Such data originated from long-term observations in three patients with very different perinatal prognosis but with common final condition of a live newborn.

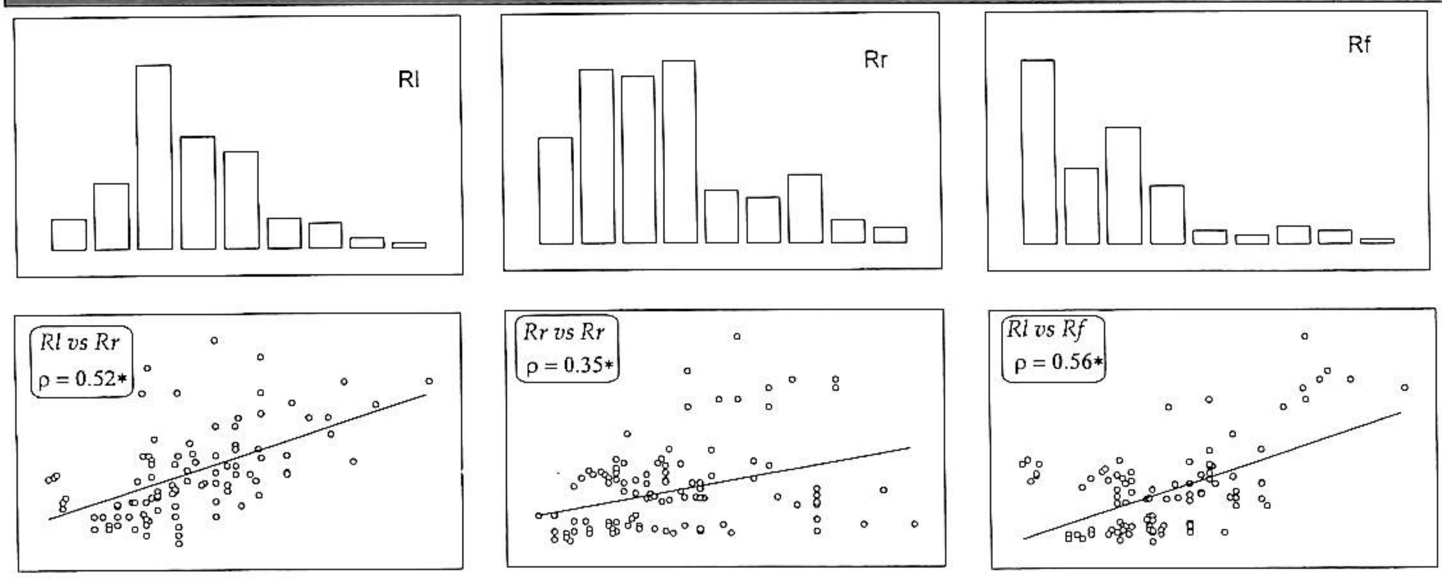
The obtained results showed a negative and high value for the slope and a high linear regression coefficient for umbilical cord resistance index. Both uterine arterial resistance indexes had moderate values in the case of favorable fetal evolution. However, for the remaining cases with risk antecedents or Rh-isoimmunization, the corresponding uterine artery resistance indexes had a more complex pattern.

The goal of this report is to study the linear correlation between umbilical cord and uterine artery resistance indexes. Also, it will show a new way of computing the total uterine resistance index. Finally, all the results will be integrated to account for the different prognosis stratification of the three patients involved in this longitudinal prospective study.

I. Observational Design, Patients and Method

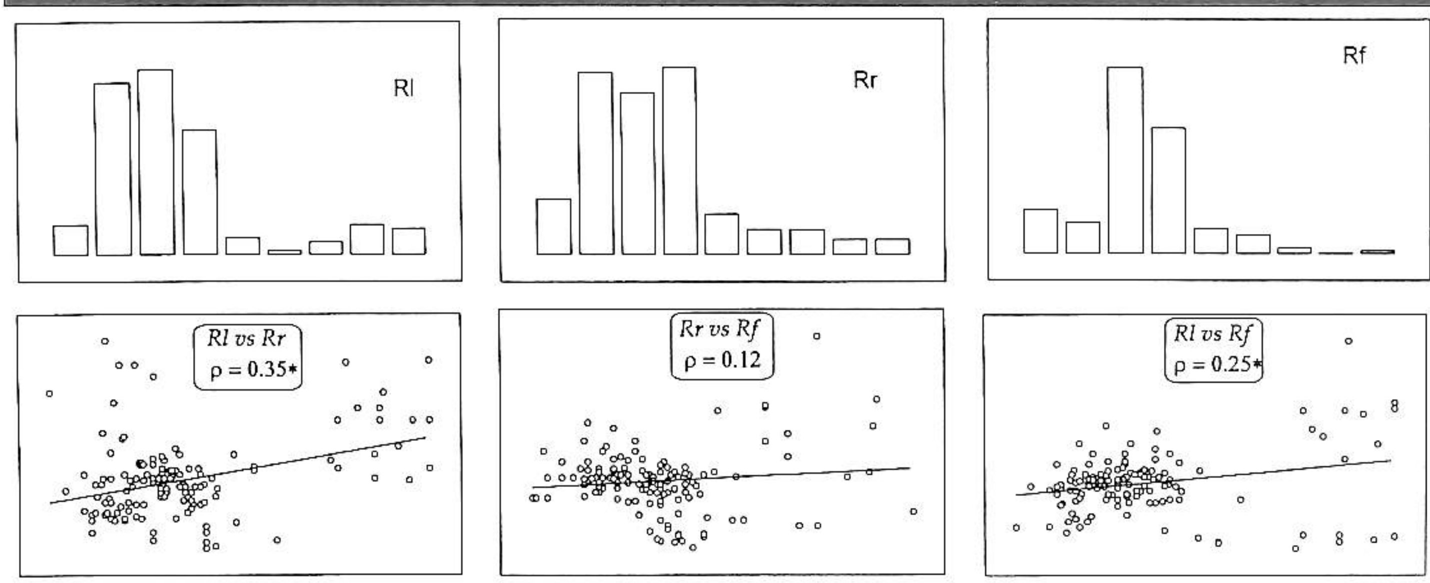
The observational design was described in detail in the first part of this study. In brief, from 15 recruited patients, three patients with evidently different stratum prognosis were selected. This clinical protocol was approved by the Ethical and Research Committee conforming with the established international procedures for Human

GRAPH 1A: PATIENT A. LINEAR CORRELATION COEFFICIENTS FOR THE LEFT UTERINE (LF), THE RIGHT UTERINE (RR) ARTERIES AND THE UMBILICAL CORD (RF) RESISTANCE INDEXES.



* $p < 0.05$

GRAPH 1B: PATIENT B. LINEAR CORRELATION COEFFICIENTS FOR THE LEFT UTERINE (LF), THE RIGHT UTERINE (RR) ARTERIES AND THE UMBILICAL CORD (RF) RESISTANCE INDEXES.



* $p < 0.05$

investigation, and informed consents' couples were included.

Initial State, Perinatal Evolution and Late Perinatal Results [4]

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, ie, its clinical classification, treatment, complications and/or sequelae. If the disease was not present, the description consisted of hereditary-familiar antecedents, pathological and non-pathological antecedents, and gynecological data that established the actual risk factors for the patient.

The risk conditions were defined as follows:

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

2. Patient with a clinically healthy perinatal condition with previous repeated-abortion antecedents

3. 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.

The standard medical treatment for these clinically healthy patients included: monthly appointments, laboratory analyses and ultrasonography imaging. The ultrasonography studies permitted detection of intrauterine retarded fetal growth alterations, macroscopic congenital malformations, placental location and maturation, and qualitative appreciation of the amniotic fluid. 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.

II. Equipment, Measurement Technique and Registration Procedure

Simple Doppler velocimetry using a 4-MHz transducer was used. During the registration the display monitor permitted identification and recording of measurements of the characteristic waveforms for the uterine and umbilical arteries, giving the resistence index values for the events previously selected using the calipers.

In each session, resistance indexes for a time series of 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; 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 the gestation. The results of this study were analyzed later and did not influence the clinical management of the patients.

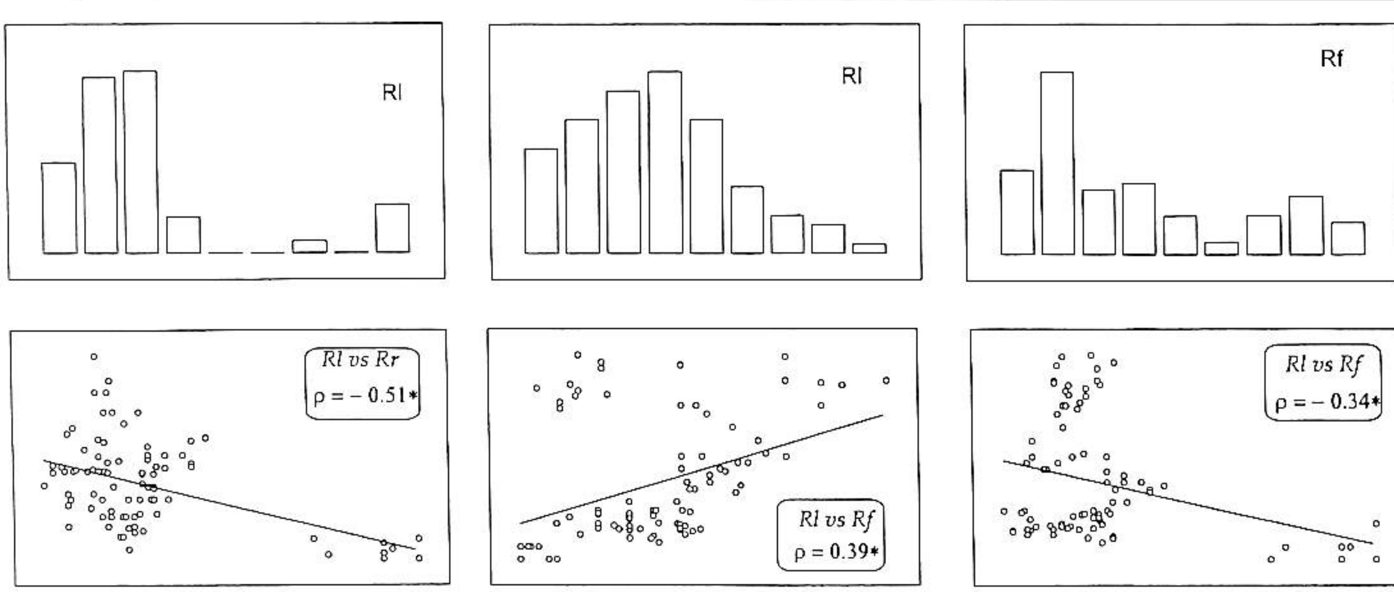
The current clinically healthy perinatal condition was established if none of clinical procedures, was capable of identifying some pathological conditions during the whole period of observation.

III. Results

1. Statistical Estimations: Product-Moment Pearson Correlation between Explanatory Variables

The graphs 1a, 1b, 1c show the correlation values for both uterine arteries and umbilical cord resistance indexes. All

GRAPH 1C: Patient C. Linear Correlation Coefficients for the Left Uterine (Rl), the Right Uterine (Rr) Arteries and the Umbilical Cord (Rf) Resistance Indexes.



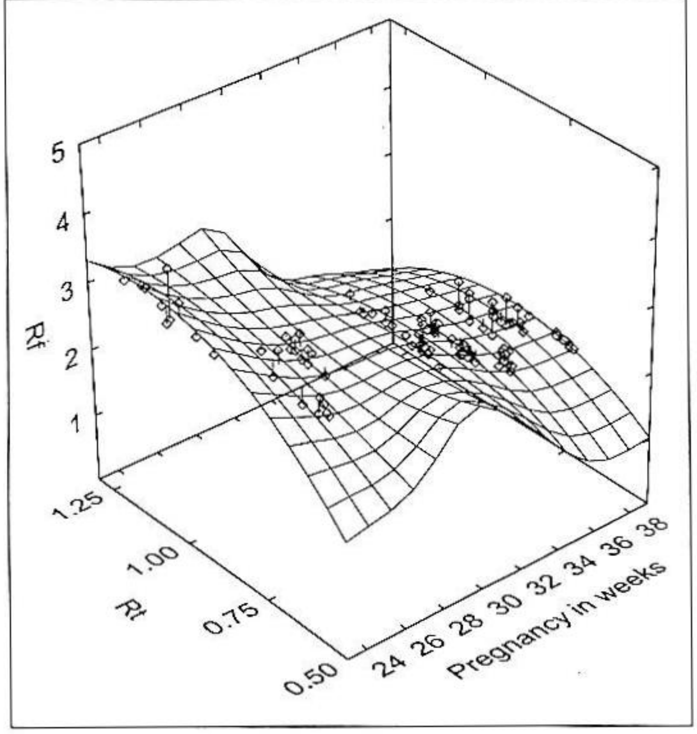
* $p < 0.05$

three patients except patient B, have moderate positive correlation values ($\rho_a = 0.52, \rho_c = 0.51$) between right and left uterine vessels.

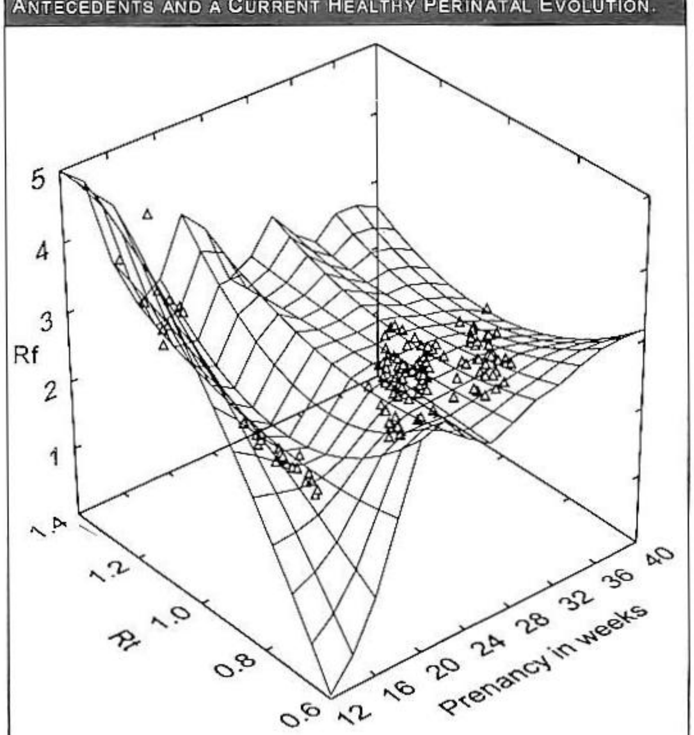
The data for patient A shows that only the left uterine artery and umbilical cord resistance indexes have high positive correlation values. There is a relatively moderate concentration of points in the initial values of delay.

Notice, that patient B shows the fewest positive correlation values in all the comparisons. Also, notice the very high concentration of points for the initial values of delay.

GRAPH 2: TOTAL UTERINE ARTERIES AND UMBILICAL CORD RESISTANCE INDEXES IN PATIENT A WITH NO RISK ANTECEDENTS AND A HEALTHY PERINATAL EVOLUTION.



GRAPH 3: TOTAL UTERINE ARTERIES AND UMBILICAL CORD RESISTANCE INDEXES. PATIENT B, WITH REPEATED ABORTION ANTECEDENTS AND A CURRENT HEALTHY PERINATAL EVOLUTION.



The data of patient C has a very heterogeneous pattern with moderate negative correlation values for both uterine resistance indexes, a moderate negative correlation value between the left uterine resistance and the umbilical cord resistance and a very high concentration of points. Also, it presents a low positive correlation between the right uterine resistance and the umbilical cord resistance.

These graphs confirm the diversity observed in the resistance index histogram. In some cases the data became significant concerning the normal, log-normal or gamma distributions.

2. Total Uterine Resistance Index and Non Parametric Test

As a consequence of the high correlation coefficients of both uterine arteries, a redundancy of information should be suspected in the variables and which may be corrected using some form of calculated total resistance. In the literature reports there is a common practice that consists of computing the total uterine resistance index by directly adding the left and right uterine resistance indexes as if these vessels were anatomically arranged in series, in fact, the left and right uterine arteries are arranged in parallel [5]. Hence, the total resistance index (R_T) should be calculated by adding the inverse values for each of the resistance values [6].

Graphs 2, 3 and 4 show 3-D dispersion plots for the total uterine resistance index (R_T), the umbilical cord (R_F) and the pregnancy in weeks for each patient. In these graphs, each point is the value of ten measurements taken for each vessel on a given date.

A paired comparison with a time basis of 28, 32 and 34 weeks of gestation was performed with the Friedman-Anova rank test for repeated measurements [7] which resulted in:

	VARIABLES	N	D. F.	χ^2	P <
RF	PATIENTS A, B, C	30	2	51.4438	0.00001
RT	PATIENTS A, B, C	30	2	31.2667	0.00001
D.F.- DEGREES OF FREEDOM					

The above values can be interpreted as statistically different for the weeks that can be compared.

3. Non Linear Adjustment

Non linear exponential smoothing was obtained using Quasi-Newton function minimization procedure to mean absolute percentage error (MAPE) [8, 9]. The model includes the following components: a constant parameter (α), a linear trend (γ), a damped trend (Φ), and the time of gestation.

The Umbilical Cord Resistance Index

Table 1 shows the components of the exponential model. Note the increasing values in the constant parameter (α) in relation to the increasing risk of the patient (recall that patient A had the lowest risk). The linear participation (γ), is easily identified for patient A, and its influence decreases as the risk of the patient increases. The damped trend has a discreet and similar value found in all three patients.

Uterine Indexes: Individual Versus Total

The redundancy of uterine values was suggested by high correlation coefficient and is confirmed by the same values repeated in the constant parameter, the linear trend and the damped trend for each uterine arterial resistance indexes, as is observed in the tables 2.

Table 3 shows the total in-parallel-uterine resistance indexes. These values exhibit very similar values in the adjusted components.

IV. Discussion

Values for arterial resistance indexes in cross-observational studies have been reported previously. However, there are no reports of long-term studies that take into account the all the antecedents of a pregnant patient, the perinatal evolution and the late postpartum period.

The principal aim of this report is to study the statistical variability of the uterine arterial and umbilical cord resistance indexes obtained from three patients with very different clinical prognosis, each one ending with an alive newborn, with a different corresponding level of health. The reasoning behind this long-term approach considers the statistical variability evidenced by the biological strategies that contend with the difficulties of presenting in the initial and subsequent conditions of the patients.

This second part constitutes the complementary study of the statistical properties of the resistance indexes obtained by simple Doppler. The results presented here support the presence of collinearity between uterine indexes, as the high linear correlation coefficients suggest. However, the data do not fulfill the premises of randomness, homoscedasticity, and non correlation, hence there is a serious limitation on the validity of the linear approach.

Adding the reciprocal values of the left and right uterine resistance may give an appropriate estimate of the total resistance and would overcome such collinearity.

To confront the non linear nature of the data and to evaluate the impact of the total calculated resistance, a nonlinear exponential smoothing with Quasi-Newton function minimization procedure to mean absolute percentage error (MAPE) was utilized. The model includes the following components: a constant parameter (α), in the case of $\alpha_{\to 0}$ where the effects previously observed will disappear slowly, that is, small α value will only follow the major trend. The linear component trend is accounted by γ. The damped trend Φ indicates how quickly the trend will be damped or increased.

With the previous criteria in mind, the results presented in table 1, 2 and 3 can be interpreted as follows:

a) The umbilical cord resistance index. As the risk factor of the patient increases, the (γ) linear trend participation vanishes and the constant parameter (α) acquires its maximum value, indicating that the trend is greatly influenced by even minor disturbances, this reflect a more biological vulnerability. This can be true especially in the RH-isoimmunized patient (patient C). See table 1.

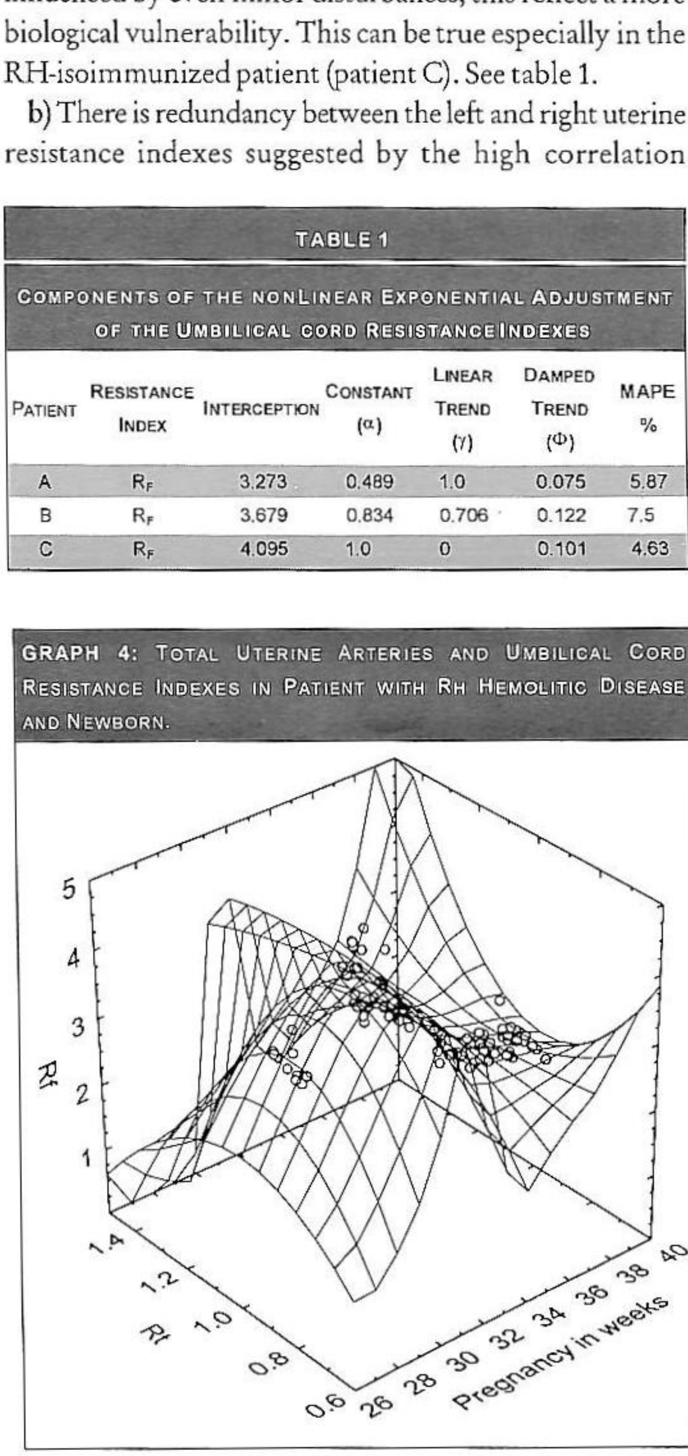
b) There is redundancy between the left and right uterine resistance indexes suggested by the high correlation

TABLE 1

COMPONENTS OF THE NONLINEAR EXPONENTIAL ADJUSTMENT OF THE UMBILICAL CORD RESISTANCE INDEXES

PATIENT	RESISTANCE INDEX	INTERCEPTION	CONSTANT (α)	LINEAR TREND (γ)	DAMPED TREND (Φ)	MAPE %
A	R_F	3.273	0.489	1.0	0.075	5.87
B	R_F	3.679	0.834	0.706	0.122	7.5
C	R_F	4.095	1.0	0	0.101	4.63

GRAPH 4: TOTAL UTERINE ARTERIES AND UMBILICAL CORD RESISTANCE INDEXES IN PATIENT WITH RH HEMOLITIC DISEASE AND NEWBORN.



coefficients and confirmed by very similar values for the α, γ and Φ components shown in table 2.

c) Note also, such adjusted non linear component of the left and right uterine resistance are almost identical to the corresponding total uterine parallel resistance, as can be verified in table 3. This implies that such calculated total resistance do not appear to corrupt the basic information contained in the data.

At this point, we can contrast the values of our R_F and R_T estimates are different through the non parametric test. The Friedman-Anova rank test suggests a significant statistical difference between the patients (in those where a comparison was possible). However, the picture is incomplete because the major part of the remanding data can not be compared due to the different duration of each gestational period.

1. Comment

How do we justify an extended version of the methodological essay, as this work? One part of the answer is specific and is due to the proper non linear and non parametric nature of the data. This obliges one to first use linear tools to explore and use exhaustively the initial possibilities and then recur to non linear approximation.

On the other hand, there exists a general aspect to the answer. Although there is an increasing tendency to use statistical tests to validate our scientific knowledge, there is no adequate validation for the premises of such tests.

For example, a recent study examines the reported articles in a prestigious medical journal on a temporal comparative basis, finding that ~ 90% of the articles that used statistical tests made no mention of any of these assumptions, < 5 % of the articles checked for normality or homogeneity of variance and only 7 to 9 % of the articles, respectively, noted specifically that the subjects were randomly assigned to groups [10]. This is very important because the misuse of statistics maybe, in fact, unethical [11, 12].

2. Limitations of this Work

A global model for resistance index array. Although these results bring a new perspective to the role of arterial resistance in the fetal environment, the information accounted for in this approach is insufficient to propose an entire model. In this aspect this work may be considered a methodological essay that, in the future, should be done under a formal experimental design (randomly sampled-representative patients, valid control group, etc.) and probably using the now-at- hand Doppler pulsed color equipment. But, this present exploratory study represents the valid via to the methodological conformation.

TABLE 2

COMPONENTS OF THE NON LINEAR EXPONENTIAL ADJUSTMENT OF THE UTERINE ARTERIAL RESISTANCE INDEXES

PATIENT	RESISTANCE INDEX	INTERCEPTION	CONSTANT (α)	LINEAR TREND (γ)	DAMPED TREND (Φ)	MAPE %
A	R_L	1.432	0.913	0	0.876	6.0
A	R_R	1.672	0.913	0	0.876	5.23
B	R_L	1.861	0.913	0	0.876	5.32
B	R_R	3.004	0.913	0	0.876	7.8
C	R_L	2.304	0.913	0	0.876	6.02
C	R_R	1.624	0.913	0	0.876	5.42

TABLE 3

COMPONENTS OF THE NON LINEAR EXPONENTIAL ADJUSTMENT OF THE TOTAL UTERINE ARTERIAL RESISTANCE INDEXES

PATIENT	RESISTANCE INDEX	INTERCEPTION	CONSTANT (α)	LINEAR TREND (γ)	DAMPED TREND (Φ)	MAPE %
A	R_T	0.8964	0.914	0	0.721	4.5
B	R_T	1.149	0.913	0	0.876	4.41
C	R_T	0.9536	0.913	0	0.876	3.99

Conclusions and Perspectives

The results presented here support the idea of very different biologic strategies formed by a predominantly decreasing linear tendency of the umbilical cord resistance index for a non risk antecedent which corresponds to a patient with a low risk perinatal evolution. The presence of increasing risk factors (patient history or current pathological conditions) diminishes this decreasing linear tendency in regard to the gestation and this refers to the biological vulnerability as suggested by the non linear exponential adjusted components.

In reference to the total-in-parallel uterine resistance index, the adjusted components suggest that the viability of the pregnancy is assured at a level close to 1.0, no matter the relatively high tendency to be affected by environmental factors.

The fruitful aspects of these two reports support the plan to study, on a long-term basis, the statistical variability present in the cardiovascular materno-fetal adaptive pattern. The previous affirmations receive major validity with the incorporation of the Doppler ecocardiography color equipment used to study directly not only the arterial resistance but also the blood flow pattern through non invasive inspection of the cardiovascular maternal status.

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