Hypoxia index in the prediction of abnormal CTG at delivery in uncomplicated pregnancies

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Abstract

OBJECTIVES: The evaluation of hypoxia index (HI) in the prediction of abnormal fetal heart rate at delivery in uncomplicated pregnancies.
MATERIAL AND METHODS: The study group included 148 pregnant patients at term (69 patients with and 79 without brain sparing effect). The value of C/U ratio and HI was determined. Next, its value in predicting abnormal fetal heart rate during labor was evaluated. Then the predictive value of the HI index, C/U and last abnormal values of PI and RI in the MCA and the UA were compared in relation to the analyzed parameters. Evaluation included signs of fetal distress in CTG and abnormal fetal outcome. Then selected parameters, characterizing pregnancy course and fetal outcome with abnormal Doppler indices, were compared.
RESULTS: The designated value of hypoxia index characterized by abnormal neonatal outcome was >10 for sHI and >14 for HI. Low prognostic value of MCA PI and RI, and UA PI and RI has been shown. The highest predictive value was marked by C/U and HI. There were no statistically significant differences in prediction of abnormal fetal heart rate during labor between C/U ratio, HI and sHI.
CONCLUSIONS: The C/U ratio showed the highest sensitivity in the prediction of fetal abnormal heart rate. The C/U ratio, as a easier test, should be recommended as a first-line test in the prediction of abnormal CTG recordings in uncomplicated pregnancies.

Abbreviations:

CTG	- cardiotocography
C/U	- cerebroumbilical ratio
HI	- hypoxia index
MCA	- middle cerebral artery
PI	- pulsatility index
RI	- resistance index
sHI	- mean value of hypoxia index
UA	- umbilical artery

INTRODUCTION

Standard tests used in the diagnosis of fetal distress do not identify the risk and do not allow to determine precisely the duration of abnormal conditions that the fetus is still able to tolerate. So far, tests of Doppler ultrasound have allowed the diagnosis of blood flow redistribution, but hypoxia index (HI), discovered by Arbeille *et al.* (1998) can also specify the severity of hypoxia and its duration. Hypoxia index can also be useful in the prediction of abnormal neonatal outcome in

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pregnancies complicated by malaria, hypertension and chronic fetal hypoxia (Arbeille *et al.* 1998; 2002; 2005). Jugović et al., showed that hypoxia index is a good indicator in the prediction of brain damage in fetuses who have undergone chronic hypoxia. This was confirmed by ultrasound brain assessment after delivery (Jugowić *et al.* 2007). Hypoxia index is calculated by summing the daily reduction in C/U ratio below the cut-off value over the period of observation (in percent below the cut-off value 1.1). The obtained value of the index indirectly reflects the degree of hypoxia, the cumulative relative deficit in pO_2. Application of HI may be helpful in targeting patients who will show abnormal fetal heart rate during labor and abnormal fetal outcome.

AIM

To assess the hypoxia index in the prediction of abnormal fetal heart rate during labor. Objective was realized through the designation of HI values in the term uncomplicated pregnancy and the determination the predictive value of the HI index in predicting fetal heart rate abnormalities during labor. Results were analyzed by comparing the predictive value of the HI index and C/U ratio in relation to selected parameters characterizing pregnancy course and neonatal outcome.

MATERIALS AND METHODS

The study was conducted between 2007 to 2010, in uncomplicated pregnancy. Gestational age ranged between 37 and 42 completed weeks of gestation. The study included 148 patients, among them 101 delivered after 40 weeks and 73 after 41 weeks. Patient age ranged from 17 to 45 years. Duration of pregnancy was determined on the basis of the last menstrual period and ultrasound examination in the first trimester. The study group included 69 patients fulfilling the criteria for brain sparing effect and 79 with no markers of brain sparing. The study was approved by the medical ethics review board and all patients gave informed consent. Doppler blood flow studies were performed using the apparatus of GE Logic 5 Pro, equipped with a transducer 3.5 and 5.0 MHz, with the option of pulse wave and color Doppler. Doppler blood flow studies were performed in the umbilical artery (UA) and middle cerebral artery (MCA). Measurements were performed daily by calculating RI, PI and the cerebroumbilical ratio (C/U). The analysis included the last measurement before delivery. The blood flow redistribution was defined on the basis of C/U value. The C/U ratio was defined according to Arbeille, by calculating the ratio of MCA RI/UA RI. Only the values <1.1 were considered abnormal (Arbeille *et al.* 2005). Hypoxia index was calculated by summing the daily reductions in C/U ratio (in percent below the cut-off value of 1.1) over the period of observation. The mean value of the HI (sHI) was the sum of the daily reductions in C/U ratio divided by the number of days. Figure 1 and 2 illustrate an example of how to calculate the sum and mean HI (HI and sHI).

During delivery continuous CTG monitoring was carried out. Assessment included the following markers of fetal abnormal heart rate occurring in the last CTG recordings:

1. late and variable decelerations (at least three decelerations within 30 minutes)
2. narrow or silent oscillation – low variability (lasting at least 40 minutes or longer)
3. basic fetal heart rate (>150 bpm or <110 bpm lasting at least 10 minutes) according to the FIGO recommendations (Rooth 1987).

Newborn assessment was carried out based on the Apgar score and acid-base balance parameters from umbilical cord blood. We analyzed the following param-

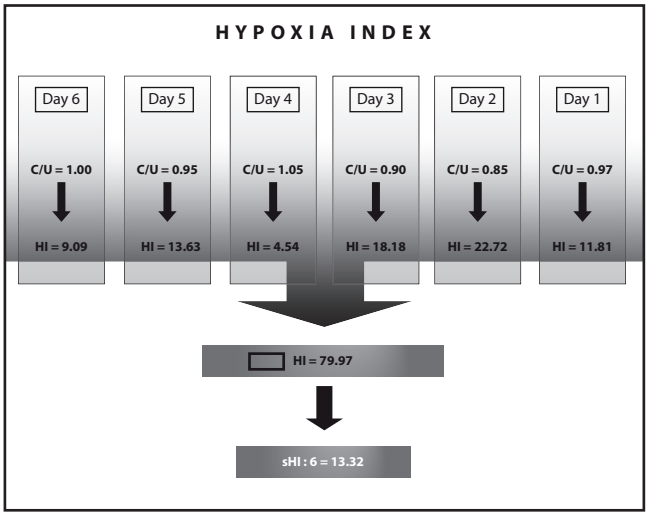

Fig. 1. The method of determining the sum (HI) and mean of HI (sHI).

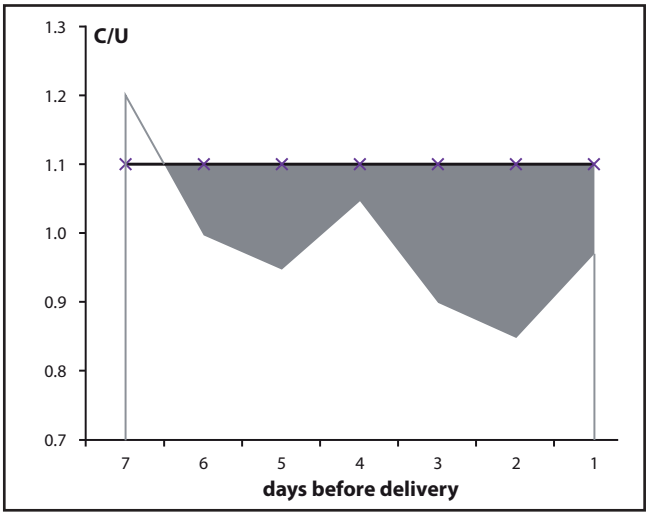

Fig. 2. Determination of HI. The value of HI corresponds to the area between the percentage C/U ratio curve and the time axis in days.

eters: maternal age, obstetric history, gestational age at birth, Apgar scoring at 1 and 5 minutes of life, pH, BE, pO_2 and pCO_2 in the umbilical artery, the prevalence of abnormal fetal outcome and the mean birthweight and prevalence of green amniotic fluid. We also evaluated the pregnancy course in terms of the incidence of cesarean delivery with particular emphasis on operations performed because of fetal distress. Then, selected parameters, characterizing pregnancy course and fetal outcome, have been compared with abnormal Doppler studies. The prognostic value of abnormal parameters characterizing blood flow in relation to selected parameters determining the pregnancy course, neonatal outcome and abnormal fetal heart rate during labor have been also assessed.

The analysis included the following parameters: pH (pH<7.2 was considered abnormal), BE (abnormal results were below - 12 mEq/L); pO_2 (abnormal results were less than 15 mmHg), pCO_2 (abnormal values were above 45 mmHg). Abnormal fetal outcome was defined on the basis of three criteria:

- Apgar score at 5th minute <7 pts. or
- pH <7.20 or
- BE ≤ 12 mEq/l.

Statistics

Parameters expressed on an interval scale, such as age, gestational age, body weight, pH, pCO_2, pO_2, BE, C/U, HI, have been described as the arithmetic mean and standard deviation. The compliance of those parameters with normal distribution with the Shapiro-Wilk test was analyzed. For parameters consistent with the normal distribution to compare between the two groups Student's t-test for independent variables was used when the variances in the samples were homogeneous, otherwise the Welch test was used. When compliance with the normal distribution has not been confirmed, nonparametric Mann-Whitney test was used. Apgar score at 1 and 5 minutes expressed on an ordinal scale described median, minimum and maximum values and the Mann-Whitney nonparametric test was used to compare two independent groups. Parameters expressed in nominal scale were depicted as the number of newborns in each category and the corresponding percentage. Contingency tables were determined as a composite of two parameters at nominal scale. Chi2 test with Yates' correction or Fisher exact test were used to investigate the relationship between these parameters in the tables 2×2. The evaluation was performed for the following levels of significance: $p<0.05$, <0.01, <0.001. The pulsatility and resistance indices were coded on the normal and abnormal values. These categories accounted for the test. The comparison with the parameters of the newborn assessment, the number of true positive, true negative, false positive and false negative cases has been determined. Than sensitivity, specificity, positive predictive value and negative predictive value were defined. Assessment of the predictive value of HI in relation to abnormal neonatal status was based on ROC curves (Receiver Operating Characteristic Curve). Calculations were performed using the statistical package STATISTICA (data analysis software system) version 8.0 (StatSoft, Inc.2007), your package GraphPad Instat Software, and Analyse-it for Microsoft Excel v. 2.2.

RESULTS

The cut-off value of the mean HI determined by ROC curves for abnormal fetal outcome was 10. Comparing the group with HI >10 and <10, patient age, gestational age at admission and during delivery have been found not to differ between the analyzed groups. No statistically significant differences in relation to the delivery mode has been noted between groups. The percentage of urgent cesarean sections also did not differ significantly (data not included). In the group of patients with sHI >10, a significantly higher incidence of abnormal CTG records compared to the second group was observed (Table 1).

The cut-off value for the sum of the HI in relation to the abnormal fetal outcome was 14. Patient age, gestational age at admission and during labor did not differ significantly in the analyzed groups. The study showed no statistically significant differences in the delivery mode. The prevalence of urgent cesarean sections was higher in patients with HI>14 (26.3%) when compared to HI≤14 (8.8%) (Table not included). In patients with HI>14 significantly more abnormal CTG records (66.7%) were noted when compared to the HI≤4 group (21.9%). In the group of HI>4, detailed analysis of fetal heart rate abnormalities demonstrated a significantly higher number of episodes of bradycardia (14.0%), late decelerations (24.6%), variable decelerations (33.3%) and a narrow or silent oscillation (24.6%) than in the second group. The study showed no statistically significant differences in tachycardia episodes (Table not included).

The value of analyzed tests was assessed in predicting abnormal fetal heart rate during labor.

Comparison of tests demonstrated that the use of the C/U ratio in predicting abnormal fetal heart rate

Tab. 1. Analysis of abnormal fetal heart rate during labor.

	sHI>10 n=58	sHI≤10 n=90	*p*-value
Abnormal CTG (n)%	(41)70.7	(17)18.9	0.0001
Bradycardia (n)%	(8)13.8	(1)1.1	0.0025
Tachycardia (n)%	(11)19.0	(4)4.4	0.0096
Late decelerations (n)%	(15)25.9	(2)2.2	0.0001
Variable decelerations (n)%	(17)29.3	(12)13.3	0.0204
Narrow or silent oscillation (n)%	(17)29.3	(6)6.7	0.0003

Fisher exact test 2-sided

Tab. 2. Sensitivity, specificity, positive and negative predictive value, likelihood ratio od analyzed tests in predicting abnormal fetal heart rate during labor.

	Test	Sensitivity (%) 95% PU	Specificity (%) 95% PU	Positive predictive value (%) 95% PU	Negative predictive value (%) 95% PU	Likelihood Ratio
CTG	C/U	74.1 0.61–0.85	71.1 0.61–0.80	62.3 0.50–0.74	81.0 0.71–0.89	2.6
	sHI	70.1 0.57–0.82	81.1 0.71–0.89	70.1 0.57–0.82	81.1 0.71–0.89	3.7
	HI	65.5 0.52–0.77	78.9 0.69–0.87	66.7 0.53–0.79	78.0 0.68–0.86	3.1
	MCA RI	12.0 0.05–0.23	91.1 0.83–0.96	46.7 0.21–0.73	61.6 0.53–0.70	1.3
	MCA PI	56.9 0.43–0.70	77.8 0.68–0.86	62.3 0.48–0.75	73.7 0.64–0.82	2.6
	UA RI	32.8 0.21–0.46	87.8 0.79–0.94	63.3 0.44–0.80	66.9 0.58–0.75	2.7
	UA PI	27.6 0.17–0.41	91.1 0.83–0.96	66.7 0.45–0.84	66.1 0.57–0.74	3.1

Tab. 3. ROC curves - comparison of tests used in the prediction of abnormal CTG recordings.

	p-value
C/U vs HI	0.0635
C/U vs sHI	0.0830
HI vs sHI	0.6477

during delivery showed the highest sensitivity (74.1%). sHI demonstrated slightly lower sensitivity (70.1%) (Table 2). Figure 3 presents comparative analysis of the tests used in the prediction of abnormal fetal heart rate during labor.

The used tests did not differ statistically significantly in predicting the occurrence of abnormal fetal heart rate during delivery (Table 3). Comparative analysis of tests used for the various parameters of fetal heart rate abnormalities during delivery showed no statistical difference between the tests (Table not included in the text). Analysis of markers of abnormal fetal outcome also did not show statistically significant differences between the parameters except BE <-12 mEq/L (Table not included in the text).

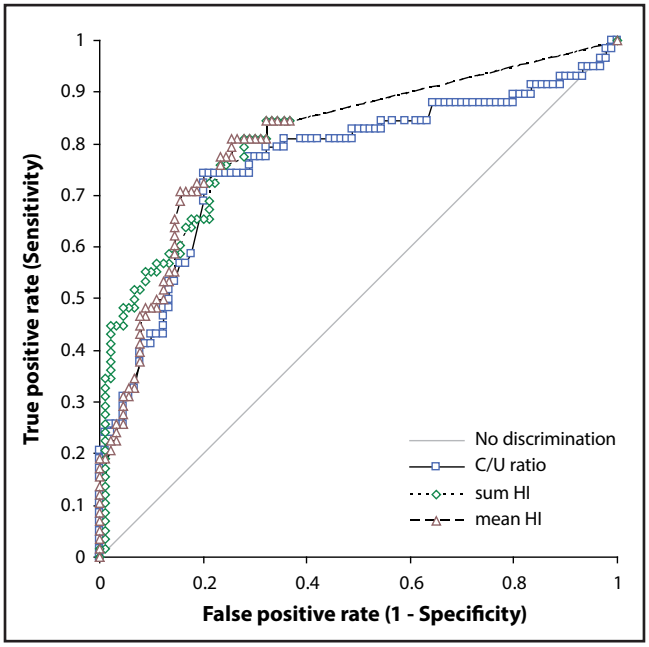

Fig. 3. Comparative analysis of the tests used in the prediction of abnormal fetal heart rate during labor. C/U: area under the curve = 0.76; 95% CI: 0.68–0.85 ($p<0.0001$ in relation to box 0.5). sHI: area under the curve = 0.81; 95% CI: 0.74–0.88 ($p<0.0001$ in relation to the area of 0.5). HI: area under the curve = 0.82; 95% CI: 0.75–0.89 ($p<0.0001$ in relation to box 0.5).

DISCUSSION

To ensure optimum safety of pregnant patients in term of effective fetal monitoring and appropriate methods of surveillance remains a major problem and challenge in modern perinatal medicine. Therefore, new methods that would allow such supervision continue to be searched for.

Hypoxia index was calculated by summing the daily reductions in C/U ratio (in percent below the cut-off value of 1.1) over the period of observation and its value indirectly reflects the degree of oxygen deficit (Arbeille *et al.* 2005). In the literature there are a few reports analyzing the use of HI in obstetrics. Arbeille et al., assessing the HI in pregnancy complicated by malaria, have found that the value of the HI index above 150 in the 10-day period of observation was associated with the occurrence of abnormal fetal heart rate during labor

and reflected the highest deficit of oxygen (Arbeille *et al.* 1998). The results have shown that fetuses have the ability to compensate for the reduced supply of oxygen without signs of fetal distress, if the oxygen deficit does not exceed 20%, which corresponds to the C/U ratio of about 0.8 by 7.5 days (Arbeille *et al.* 1998). Similar results have been obtained in studies carried out in pregnancies complicated by hypertension and chronic fetal hypoxia (Arbeille *et al.* 2005). In 2007 Jugović *et al.*, presented the results of studies on the application of the hypoxia index in the prediction of hypoxic brain damage in fetuses with intrauterine growth restriction (Jugović *et al.* 2007). The cut-off value above 74 reflected a group with sonographically detected brain injuries. The difference in cut-off values between Arbeille and Jugović may suggest that brain damage can occur even before the abnormal fetal heart rate, as well as in preserved circulatory autoregulation mechanisms. Studies by Jugović used slightly different statistical methods, and the abnormal value of the C/U ratio was defined as below 1.0, as opposed to 1.1 in the previous work. Ultrasound monitoring in the cited studies ranged from 10 to 14 days, and the obtained HI cut-off values associated with the serious intrapartal complications ranged from 74 to 150. When dividing the values by the number of days of conducted observation, it can be assumed that the mean HI above which complications may occur, ranged between 7.4–15. Cut-off value of sHI obtained in the presented study in the prediction of abnormal fetal heart rate was 10, so it was very close to the value obtained by the above mentioned authors. Therefore, we can speculate that the sHI value above these values may suggest the development of intrapartal complications. The sum of HI is difficult to compare due to the fact that the number of days of observation is an important factor that influences the final value of HI. In presented study the period of observation was much shorter, ranging from 1 to 6 days. To the best of out knowledge, at present literature offers no studies that analyze HI value in term uncomplicated pregnancy. Thus, this study is the first attempt to assess the value of HI in term pregnancy in the aspect of prediction of abnormal fetal heart rate and abnormal fetal outcome.

Assuming sHI values above 10, as a representative of the abnormal fetal outcome, there were no statistically significant differences with regard to the delivery mode between groups, as well as urgent caesarean sections. In the group with sHI>10, a significantly higher incidence of abnormal CTG recordings (70.7%) was reported when compared to the other group (18.9%) (Table 1). The prevalence of urgent cesarean sections was higher in the group with HI>14 (26.3%). Similarly, Hitschold et al., using a value of 2.3 as the cutoff value for the C/U ratio in the UA identified patients at-risk of urgent caesarean section (Hitschold *et al.* 1988). The assessed sensitivity of this parameter was 71.0% and specificity 91.0%. The value of 2.4 as the cutoff value in predicting unfavorable fetal outcome adopted Fischer et al (Fischer *et al.* 1991). The sensitivity and specificity in predicting unfavorable fetal outcome were 57.0% and 78.0%, respectively. Li and colleagues comparing the prevalence of operative deliveries due to fetal distress did no found any differences in vascular resistance in the MCA between the groups with or without fetal distress (Li *et al.* 2006). However, a direct comparison of the results presented in these studies is difficult because of the different criteria of poor fetal outcome adopted by the authors.

Comparison of the analyzed tests showed that application C/U in predicting abnormal fetal heart rate during labor presented the highest sensitivity (74.1%). (Table 2). Among applied tests, C/U ratio, sHI and HI showed the highest positive predictive value. Different results were published by Habek *et al.*, who prospectively analyzed a group of 58 IUGR fetuses, assessing the relationship between biophysical profile, C/U ratio and the antenatal evaluation of fetal heart rate in the CTG (Habek *et al.* 2007). The C/U ratio was calculated on the basis of the RI index, and values <1.0 were taken as abnormal. The authors demonstrated a statistically significant relationship between C/U≥1.0 and normal CTG recordings. However, the C/U<1.0 did not correlate with suspected or abnormal CTG. The relationship between C/U and favorable or unfavorable fetal outcome has been found as well. Adverse fetal outcome was defined as: pH <7.2, Ap at 5 min <7 points, admission to NICU, and cesarean section because of suspected fetal hypoxia.

So far, Doppler measurements have allowed the diagnosis of blood flow redistribution (Ropacka-Lesiak *et al.* 2011), whereas the HI can further evaluate the severity of hypoxia. Moreover, standard tests used in the diagnosis of fetal distress, failed to identify the degree of risk and did not allow to determine the duration of adverse conditions that the fetus was still able to tolerate. The HI was proposed in order to assess both the intensity and duration of blood flow redistribution in high-risk pregnancy (Arbeille *et al.* 2005). Results obtained by the authors suggest that the C/U ratio and sHI are characterized by the highest sensitivity in the prediction of abnormal fetal heart rate and adverse fetal outcome. However, comparing the predictive value of C/U, sHI and HI did not show the superiority of hypoxia index. It seems that the C/U, as an easier test, should be recommended as a first-line test. Similar opinion can be found in some studies that call into question the usefulness of this method, pointing to the fact that it is very time consuming and the assessment of C/U seems to be simpler and quicker to perform (Ebbing *et al.* 2007).

Many of the studies cited in the discussion are difficult to compare, mainly because of different criteria used in these works. Firstly, many authors use different grading scales of CTG records under different guidelines that which can be found in the literature (Rooth *et al.* 1987, RCOG 2001). Another problem is

the methodology of calculating the C/U ratio, which in certain papers is calculated on the basis of PI, in others on RI, and in yet other papers on the S/D. Comparison is even more difficult because of the adoption of different cut-off values accepted as abnormal. Values less than 1.0 (Jugović *et al.* 2007), 1.08 (Gramellini *et al.* 1992; Wladimiroff *et al.* 1987), 1.05 (Devine *et al.* 1994) 1.1 (Arbeille *et al.* 2005), as well as based on percentile grids, can be found in the studies (Bahado-Singh *et al.* 1999; Baschat & Gembruch 2003; Ebbing *et al.* 2007). A variety of rules defining the adverse fetal outcome brings even more confusion. It covers many different parameters, depending on the analyzed study, starting with Apgar score, acid-base balance, by the admission to the NICU, occurrence of complications such as intraventricular hemorrhage, infection, etc.

In summary, our knowledge of the application and the predictive value of Doppler parameters in the monitoring and prediction of fetal outcome at term is still questionable and incomplete. It seems that Doppler blood flow assessment in uncomplicated pregnancy, especially after 40 weeks gestation, can be used to differentiate between pregnancies that could continue to be carried out conservatively, and those for which induction of delivery could be a better option. However, in order for Doppler studies to be reliable, it is important to establish normal reference curves, which allow for proper classification of the obtained results.

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