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RESEARCH ARTICLE
НАУЧНАЯ СТАТЬЯ

Integrated 2D Doppler indices of uteroplacental and fetal blood flow in diagnosis of intrauterine hypoxia

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Abstract. *Relevance*. Intrauterine hypoxia associated with placental disorders is a significant factor of ante-, intra- and postnatal fetal and newborn death. Despite clinical examination of pregnant women using ultrasound and cardiotocography, cases of intrauterine hypoxia often remain undetected prenatally. Clinical manifestation of placental disorders and intrauterine hypoxia are associated with pathological changes of blood flow resistance in the uterine, placental and fetal vessels. A combined Doppler assessment of blood flow in the uterine, placental and fetal vessels could improve detection of intrauterine hypoxia. *The aim of the study* was to assess the prognostic significance of integrated 2D Doppler indices of uteroplacental and fetal blood flow for the detection of fetal hypoxia in the 3rd trimester and to predict unfavorable perinatal outcomes. *Materials and Methods*. The outcomes of pregnancy of 48 women with fetal hypoxia delivered at 29 – 40 gestational weeks (study group), and 21 women who gave birth to healthy full-term infants (control group) were retrospectively analyzed. On the eve of delivery all women had 2D Doppler assessment of the uterine arteries, umbilical arteries, and fetal middle cerebral artery with an assessment of the cerebro-placental ratio, umbilical-cerebral ratio and cerebro-placental-uterine ratio. *Results and Discussion*. Analysis of the obtained values of cerebro-placental-uterine ratio, cerebro-placental ratio and umbilical-cerebral ratio showed the benefit from use of integrated 2D Doppler indices in the diagnosis of fetal hypoxia at 29 – 40 gestations' weeks and in predicting complications in newborns. The high sensitivity of the cerebro-placental-uterine ratio (90.5%) makes it possible to effectively use this index for the diagnosis of intrauterine hypoxia. *Conclusion.* Pathological cerebro-placental-uterine ratio < 2.44 is a clinically significant 2D Doppler criterion that predicts a high risk of asphyxia, respiratory distress syndrome, hypotrophy, and perinatal hypoxic-ischemic encephalopathy. Lower values of the cerebro-placental ratio and umbilical-cerebral ratio sensitivity (77.1% and 81.3%, respectively) limit their use for the diagnosis of fetal hypoxia as compared with cerebro-placental-uterine ratio.

Key words: Doppler assessment, uteroplacental and fetal blood flow, intrauterine hypoxia, cerebro-placental ratio, cerebro-placental-uterine ratio, placental disorders

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Introduction

Issues of gestational complications, which are associated with placental disorders, leading to the development of fetal hypoxia and the decrease in oxygen transport of mother-to-fetus, still remain topical in modern obstetrics and perinatology. Persistent fetal hypoxia leads to fetal growth restriction (FGR) and causes a conversion to anaerobic fetal metabolism that contributes to the development of acidosis and lactate accumulation, increasing the risk of ante-, intra- and postnatal death [1—3].

«Brain-sparing effect» is manifested as a compensatory response at the third trimester during fetal hypoxia and it is characterized by redistribution of blood flow to fetal brain resulting in centralization of fetal circulation with increased cerebral blood flow [4—6]. «Brain-sparing effect» leads to preferential distribution of oxygenated blood to fetal brain that allows for the maintenance of intrauterine growth and fetal development during hypoxia [7—9].

Currently, 2D Doppler ultrasound is the generally accepted standard for the monitoring of fetal status at the third trimester of gestation. However, normal Doppler ultrasound of uterine, umbilical and fetal blood flow does not guarantee favorable perinatal outcome and does not exclude hypoxic-ischemic damage in a newborn [4, 7, 8]. Cases of intrauterine hypoxia can not be diagnosed antenatally due to poor interpretation and disregard of rules for Doppler measurements of uteroplacental and fetal blood flow, ignoring a number of signs associated with fetal hypoxia (lean umbilical cord, fetal pyelectasis, blood flow alterations in several umbilical segments and etc.) and iatrogenic conditions influencing on hemodynamics of women (hypotension of pregnant women), as well as asymptomatic disease, contributing to irreversible fetal hypoxic-ischemic damages. On the contrary, overdiagnosis of placental disorders and fetal hypoxia based on Doppler measurements can lead to changes in management of pregnancy and delivery, no evidence-based treatment and polypharmacy in expectant mothers [10—12]. Thus, it is necessary to search for new predictors of fetal hypoxia based on an integration of several 2D Doppler indices for promptly change of pregnancy management and choose the mode of delivery in order to prevent severe ischemic complications and children's disability.

One of the integrated 2D Doppler indices of fetal-placental blood flow is the cerebro-placental ratio (CPR), which is calculated as the ratio of resistance indices of fetal middle cerebral artery to umbilical artery, or as the ratio of pulsatility indices of the above-mentioned vessels [6—8]. CPR less than 1 indicates the centralization of fetal circulation at the third trimester, allowing for prediction the risk of FGR, asphyxia and respiratory distress syndrome in newborns, delivery by caesarean section for fetal reasons with the admission of newborns to the neonatal intensive care unit for treatment [2, 4, 13]. Researchers have noted that CPR has low predictive value for perinatal outcomes closer to the full-term pregnancy that makes us search for more informative predictors of hypoxia [8, 14, 15].

Recently, some researchers are focused on umbilical-cerebral ratio (UCR), which is reciprocal indicator of CPR, calculated as the ratio of resistance indices of umbilical and middle cerebral arteries and, according to Acharya G. et al. [14], UCR is more useful for diagnosing of fetal hypoxia.

In the literature, there are data available for possibilities for antenatal diagnosis of fetal hypoxia based on cerebro-placental-uterine ratio (CPUR), which is integrated Doppler index [16]. CPUR is calculated as the ratio of CPR value to the mean of resistance indices of the right and the left uterine arteries. CPUR requires further study, because its threshold values at the third trimester had not yet been clarified, below which should be diagnosed with hypoxic-ischemic damage of the fetus and initiate to the delivery.

Thus, integrated 2D Doppler indices of uteroplacental and fetal blood flow (CPR, UCR, CPUR) require to define threshold limits at different periods for diagnosis of fetal hypoxia and prediction of unfavorable perinatal outcomes at gestation.

The aim of the study was to define threshold values of integrated 2D Doppler indices of uteroplacental and fetal blood flow (CPR, UCR, CPUR) for the detection of fetal hypoxia at the 3rd trimester and the prediction of unfavorable perinatal outcomes.

Materials and methods

Pregnancy outcomes and 2D Doppler indices of uteroplacental and fetal blood flow prior to the delivery were analyzed in 48 patients with fetal hypoxia, delivered at 29—40 weeks of gestation (study group), as well as in 21 women who gave a birth to healthy full-term newborns (control group). The study was approved by the clinical trial ethics committee (13.04.2021 № 4). All study participants provided voluntary informed consent to participate in the study and the processing of personal data in accordance with the World Medical Association's Declaration of Helsinki (WMA Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects, 2013). Inclusion criteria for the study were: singleton pregnancy, absence of chromosomal abnormalities. The study group included women whose newborns had retarded growth and malnutrition (P 05) with the decrease in ponderal index, signs of intrauterine hypoxia (P 20), impaired cerebral status (P 91) with perinatal hypoxic ischemic encephalopathy according to the 10th revision of the International Classification of Diseases.

Verification of fetal growth restriction (FGR) was using ponderal index for a newborn, which is the norm should be 2.4 to 12 months: less than 2.0 in cases of FGR at 29—37 gestations' weeks and less than 2.25 — after 37 weeks. The assessment of newborns was based on clinical manifestation using Apgar score and the acid-base state (ABS) of capillary blood from newborn's heel, which was determined using gas analyzer Radiometer (ABL 800 FLEX, USA) at 5—8 minutes of the child's life. Insufficient tissue oxygenation and severity of hypoxia in capillary blood of a newborn were indicated by: pathological acidosis with pH < 7.25, lactate levels more than 3.0 mmol/L [10, 11]. To assess of uteroplacental and fetal blood flow, all women prior to the delivery underwent 2D Doppler measurements of uterine and umbilical arteries, middle cerebral artery of a fetus using Voluson 730 Expert machine (GE, Healthcare, Austria) with a curved-array transabdominal transducer (AV 2—7, 2—7 MHz). 2D Doppler indices of uteroplacental and fetal blood flow were analyzed: resistance indices values of uterine and umbilical arteries, fetal middle cerebral artery, CPUR, CPS, UCR. We used the classification of uteroplacental blood flow disorders by A.N. Strizhakov et al. [17—19] to describe the results of 2D Doppler ultrasound.

Statistical analysis was performed using SPSS Statistica v10.0 and software AtteStat. Nonparametric analysis was applied with a description of median (Me) and interquartile range (25—75 %) for nonparametric distribution. Comparison of data of study and control groups was performed using the $\chi 2$- test with Yates' correction, Mann-Whitney U-test. ROC analysis (Receiver Operating Characteristic) was performed to identify the risk of fetal hypoxia at 29—40 gestations' weeks according to the data of 2D Doppler measurements of uteroplacental and fetal blood flow by calculating optimal threshold values for CPUR, UCR and CPR. Sensitivity and specificity with the description of the 95 % confidence interval were calculated to interpret the predictive effectiveness of the diagnostic method. P-values of 0.05 or less were considered to indicate statistical significance.

Results and discussion

42 (87.5 %) women had operative delivery in the study group, and of these, 35 (72.9 %) had cesarean section which has been performed remote from term for the following indications: progressive fetal hypoxia with abnormal umbilical blood flow down to absence of end-diastolic flow in 25 (52.1 %), mild and severe preeclampsia in 8 (16.7 %), premature rupture of membranes in 2 (4.1 %) cases of a breech.

FGR was verified using pathological decrease of ponderal index in 19 (39.6 %) newborns of the study group, and of these, 12 children until 37 weeks and 7 newborns after 37 weeks. In the study group 25 (52.0 %) children were born in asphyxia with Apgar score less than 7 points. There were cerebral status disturbances in 28 (58.3 %) newborns of the study group: adaptation disorders with a predominance of brain damage in 7 (14.6 %), cerebral excitability in 7 (14.6 %) and cerebral depression in 14 (29.2 %) cases. As shown in Table 1, acidosis was detected in more than half of newborns in the study group, and of these 19 (39.6 %) had moderate acidosis (pH 7.10—7.24) and 7 (14.6 %) — severe acidosis (pH <7.10).

Table 1

Incidence of blood acidosis and lactatemia in newborns in investigated groups

Acid-base state of blood	Study group (N= 48)	Control group (N = 21)	P-value
Acidosis	26 (54.2 %)	0	0.00006
Lactatemia (> 3 mmol/l)	33 (68.8 %)	5 (23.8 %)	0.001
Lactatacidemia	15 (31.2 %)	0	0.009

A few days before the delivery 2D Doppler ultrasound data on disrupted uteroplacental blood flow and abnormal fetal cerebral circulation in the study group were registered 3.8 times more than in controls (72.9 % versus 19.1 %, p = 0.00003). However, as shown in Table 2, incidence of different degrees of disrupted uteroplacental blood flow according to the classification of A.N. Strizhakov et al. [17] and abnormal cerebral blood flow in investigated groups was not significantly different.

Thus, when registering IA and IB degrees of disrupted uteroplacental blood flow the sensitivity of 2D Doppler ultrasound in diagnosis of fetal hypoxia was limited to 43.5 % (p>0.05), and when detecting II and III degrees of disrupted blood flow, it was less than 45.8 % (p<0.01) provided that the specificity not exceeding 85.0 % (p>0.05). Other researches had previously described low sensitivity of 2D Doppler assessment of blood flow in uterine and umbilical arteries separately (27.1—32.6 %) during fetal hypoxia [11, 18, 19]. Accordingly, Doppler ultrasound picture in separate maternal or fetal vessels does not always make clear the state of fetal health. So, a decrease in blood flow resistance of middle cerebral artery below the 5th percentile can be identified both in cases of fetal hypoxia, when the effect of «brain sparing» appears, and in cases of fetal hypertension [4, 5, 9]. This approach to assessment of uteroplacental and fetal blood flow in separate maternal or fetal vessels limits interpretation of the measurement results and reduces informative value of 2D Doppler ultrasound regarding the prediction of adverse perinatal outcomes in fetal hypoxia.

Table 2

Incidence of disrupted uteroplacental and abnormal fetal blood flow according to 2D Doppler assessment at 29—40 gestations' weeks in investigated groups

Variants of disrupted uteroplacental and fetal blood flow	Study group (n= 48)	Control group (n = 21)	P-value
IA degree (RIUtA> 95th percentile)	10 (20.8 %)	3 (14.3 %)	0.76
IB degree (RIUA> 95th percentile)	5 (10.4 %)	0	0.30
II degree (RIUtA and RIUA> 95th percentile)	11 (22.9 %)	1 (4.8 %)	0.68
III degree (absent or reverse diastolic blood flow in umbilical artery)	9 (18.8 %)	0	0.08
Abnormal cerebral blood flow (RIMCA< 5th percentile)	9 (18.8 %)	0	0.08

Note: RIUtA — resistance index of uterine arteries, RIUA — resistance index of umbilical artery, RIMCA — resistance index of middle cerebral artery

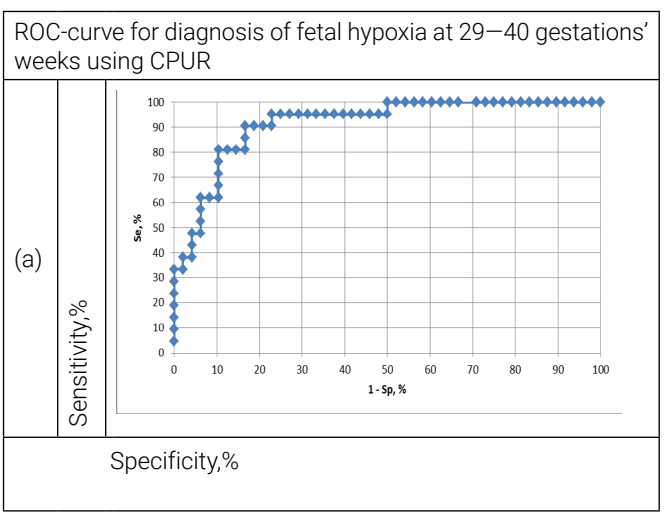
The study of integrated 2D Doppler indices accounting for uteroplacental and fetal blood flow parameters in total, have found that CPUR value significantly was decreased by 30.6 % and CPR value reduced by 24.1 % simultaneously with an increase of UPR value by 23.6 % during fetal hypoxia in the study group (table 3).

Table 3

Values of integrated 2D Doppler indices in investigated groups

2D Doppler index, Me [25; 75]	Study group (n= 48)	Control group (n = 21)	P-value
CPUR	2.04 [0.81; 3.29]	2.94[2.05; 4.78]	<0.000001
CPR	1.07 [0.62; 1.64]	1.41[1.01; 1.71]	0.00001
UCR	0.93 [0.61; 1.61]	0.71[0.58; 0.99]	0.00002

ROC-analysis for antenatal diagnosis of fetal hypoxia at 29—40 gestations' weeks based on 2D Doppler assessment of uteroplacental and fetal blood flow have allowed to determined the optimal cut-off value of 2.44 for CPUR with the best combination of sensitivity (90.5 %) and specificity (83.3 %). The area under the ROC-curve (0.91 [0.82; 1.0], p <0.000001) have indicated a high predictive value and clinical significance of this method (Figure 1a). CPUR values lower than 2.44 were interpreted as fetal hypoxia with the high risk of perinatal complications such as asphyxia, respiratory distress syndrome, fetal growth restriction, and perinatal hypoxic-ischemic encephalopathy. The optimal cut-off value for CPR was 1.14 with sensitivity of 81.3 % and specificity of 63.0 % (p = 0.0003) and low area under the ROC-curve (0.76 [0.66; 0.85], p = 0.0003) (Figure 1b). The optimal cut-off value for UCR was 0.86 with sensitivity of 77.1 % and specificity of 67.4 % (p = 0.0002) and low area under the ROC-curve (0.77 [0.67; 0.86], p = 0.0002) (Figure 1c).



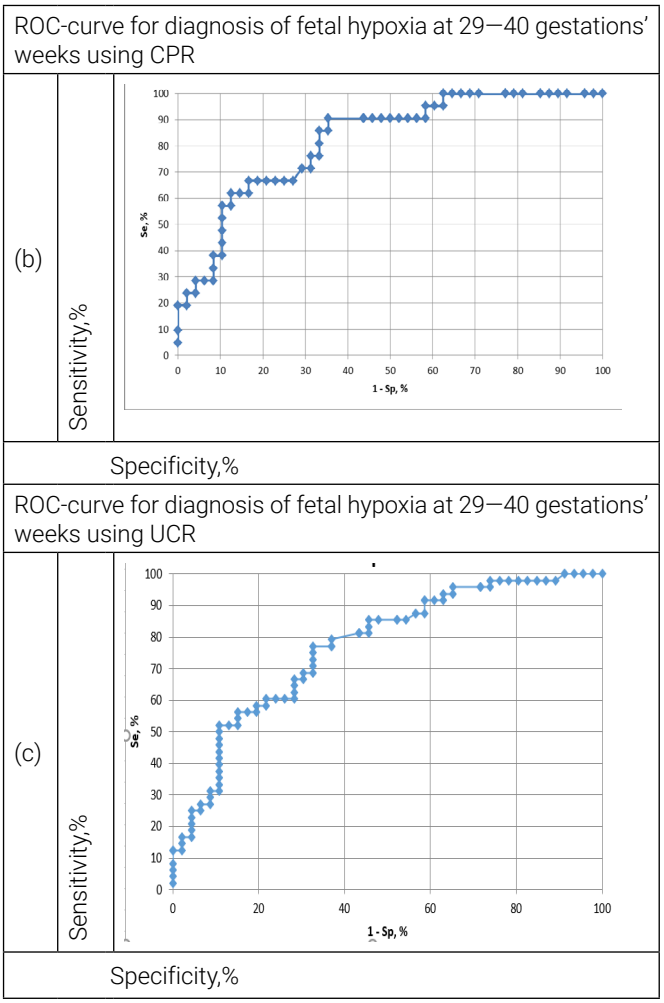


Fig. 1. ROC-curves for diagnosis of fetal hypoxia at 29—40 gestations' weeks using CPUR (a), CPR (b), UCR (c)

Conclusion

1. Abnormal integrated 2D Doppler indices (CPUR, CPR, UCR) help to identify fetal hypoxia at 29—40 weeks of gestation and anticipate of complications in newborns.

2. High sensitivity of CPUR (90.5 %) allows use this index as an effective diagnostic tool for intrauterine hypoxia. Abnormal CPUR < 2.44 is clinically significant 2D Doppler index, which allows to predict a high risk of asphyxia, respiratory distress syndrome, fetal hypotrophy, and perinatal hypoxic-ischemic encephalopathy.

3. Lower sensitivity values of CPR and UCR (77.1 % and 81.3 %, respectively) limit their use for the diagnosis of fetal hypoxia as compared with CPUR.

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Интегрированные 2D допплерометрические показатели маточно-плацентарного и плодового кровотока в диагностике внутриутробной гипоксии

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Аннотация. *Актуальность.* Внутриутробная гипоксия, связанная с плацентарными нарушениями, является значимым фактором анте-, интра- и постнатальной гибели плода и новорожденного. Несмотря на клиническое обследование беременных с применением ультразвукового исследования и кардиотокографии, случаи внутриутробной гипоксии нередко остаются пренатально не выявленными. Клиническая манифестация плацентарных нарушений и внутриутробной гипоксии связана с патологическими изменениями резистентности кровотока в сосудах матки, плаценты и плода. Сочетанная допплерометрическая оценка кровотока в маточных, плацентарных и фетальных сосудах могла бы улучшить диагностику внутриутробной гипоксии. *Целью исследования* была оценка прогностической значимости интегрированных 2D допплерометрических показателей маточно-плацентарного и плодового кровотока для диагностики гипоксии плода в III триместре и прогнозирования неблагоприятных перинатальных исходов. *Материалы и методы.* Ретроспективно были проанализированы исходы беременности у 48 пациенток с гипоксией плода, родоразрешенных в 29—40 недель гестации (основная группа), и у 21 женщины, которые родили здоровых доношенных детей (контрольная группа). Всем женщинам накануне родоразрешения произведена 2D допплерометрия маточных артерий, артерий пуповины, средней мозговой артерии плода с оценкой церебро-плацентарного соотношения, пуповинно-церебрального соотношения и церебро-плацентарно-маточного соотношения. *Результаты и обсуждение.* Анализ полученных значений церебро-плацентарно-маточного соотношения, церебро-плацентарного соотношения и пуповинно-церебрального соотношения показал результативность применения интегрированных 2D допплерометрических индексов в диагностике гипоксии плода в 29—40 недель гестации и прогнозировании осложнений у новорожденных. Высокая чувствительность церебро-плацентарно-маточного соотношения (90,5 %) позволяет эффективно использовать данный индекс для диагностики внутриутробной гипоксии. *Выводы.* Клинически значимым 2D допплерометрическим критерием, позволяющим прогнозировать высокий риск асфиксии, респираторного дистресс-синдрома, гипотрофии и перинатальной гипоксически-ишемической энцефалопатии, является патологическое церебро-плацентарно-маточного соотношения < 2,44. Более низкие значения чувствительности церебро-плацентарного соотношения и пуповинно-церебрального соотношения (77,1 % и 81,3 % соответственно) ограничивают их применение для диагностики гипоксии плода по сравнению с церебро-плацентарным-маточным соотношением.

Ключевые слова: допплерометрия, маточно-плацентарный и плодовый кровоток, внутриутробная гипоксия, церебро-плацентарное соотношение, церебро-плацентарное-маточное соотношение, плацентарные нарушения

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