https://doi.org/10.15388/vu.thesis.461
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VILNIUS UNIVERSITY

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The Significance of the Fetal Tibial Artery Doppler Examination for Predicting Perinatal Outcomes in High-Risk Pregnancy with and without Intrauterine Growth Restriction

DOCTORAL DISSERTATION

Medical and Health Sciences,
Medicine (M 001)

VILNIUS 2023

The dissertation was prepared at the Faculty of Medicine of Vilnius University between the period of 2019 - 2022.
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VILNIAUS UNIVERSITETAS

Kristina Norvilaitė

Didelės rizikos nėščiųjų vaisiaus blauzdos arterijos doplerometrijos tyrimo reikšmė vaisiaus būklės ir perinatalinių baigčių vertinimui diagnozavus vaisiaus augimo sulėtėjimą ir jo nediagnozavus

DAKTARO DISERTACIJA

Medicinos ir sveikatos mokslai,
Medicina (M 001)

VILNIUS 2023

Disertacija rengta 2019–2022 metais Vilniaus universiteto Medicinos fakultete.

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Disertaciją galima peržiūrėti VU bibliotekoje ir VU interneto svetainėje adresu:
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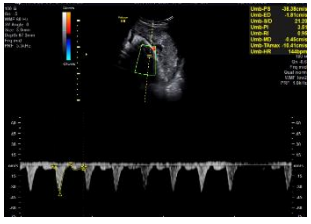
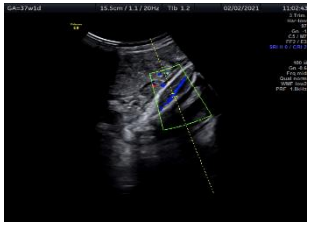
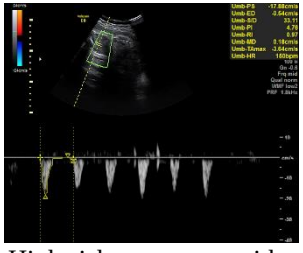
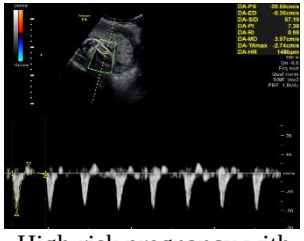
DISSERTATION AT-A-GLANCE

The aim of the study was to evaluate the prognostic value of the fetal tibial artery blood flow doppler parameters for perinatal outcomes in high-risk pregnancy with and without intrauterine growth restriction (IUGR).				
  Low-risk pregnancy group.	To measure the pulsatility indices in the fetal tibial, middle cerebral, umbilical arteries and to calculate the cerebroplacental ratio in low-risk pregnancies, and to compare the fetal surveillance tools for the prediction of perinatal outcomes.	From the 33rd gestational week to birth, on a weekly basis, the comparison of the fetal surveillance tools such as non-stress test, modified biophysical profile and of Doppler measurements of the pulsatility index in the fetal tibial (TA-PI), umbilical (UA-PI), and middle cerebral arteries (MCA-PI) was performed, and the cerebroplacental ratio (CPR) was determined.	We detected that there were no abnormal parameters in any of the fetal surveillance tools and the parameters of the analyzed arteries were within the normal range.	These findings confirmed the normal values of the fetal surveillance tools and normal PI values in all measured arteries.
 High-risk pregnancy without IUGR group.	To measure the pulsatility indices in the fetal tibial, middle cerebral, umbilical arteries and to calculate the cerebroplacental ratio in high-risk pregnancy without IUGR, to compare the fetal surveillance tools for the prediction of perinatal outcomes.	From the 33rd gestational week to birth, on a weekly basis, the comparison of the fetal surveillance tools such as non-stress test, modified biophysical profile and of Doppler measurements of the pulsatility index in the fetal tibial (TA-PI), umbilical (UA-PI), and middle cerebral	We detected that there were no significant changes in the fetal surveillance tools parameters, however, a tendency of TA-PI to a modest insignificant increase along with the increasing gestational age was observed. The parameters of	These findings can serve as an additional tool not only for the detection of the deteriorating fetal signs in high-risk pregnancies (hypertensive disorders, diabetes, cholestasis of pregnancy, COVID-19 infection) without IUGR fetus,

		arteries (MCA-PI) was performed, and the cerebroplacental ratio (CPR) was determined.	other arteries did not show significant changes	mostly in full term pregnancy cases, but also for taking a decision on the appropriate timing for the intervention in high-risk pregnancy.
 High-risk pregnancy with IUGR group.	To measure the pulsatility indices in the fetal tibial, middle cerebral, umbilical arteries and to calculate the cerebroplacental ratio in high-risk pregnancies with IUGR, and to compare the prediction of fetal surveillance tools for the perinatal outcomes.	From the 33rd gestational week to birth, on a weekly basis, the comparison of the fetal surveillance tools such as non-stress test, modified biophysical profile and of Doppler measurements of the pulsatility index in the fetal tibial (TA-PI), umbilical (UA-PI), and middle cerebral arteries (MCA-PI) was performed, and the cerebroplacental ratio (CPR) was determined	We detected that there were no significant changes in the parameters of the fetal surveillance tools, however, the increase of TA-PI was registered from the 35th week. The parameters of UA-PI did not show significant changes, while abnormal parameters in MCA and CPR showed later, from the 37th week	These findings can serve as an additional tool for detecting the deteriorating signs of the IUGR fetus and taking a decision for timely intervention in high-risk pregnancy (hypertensive disorders, diabetes, cholestasis of pregnancy, COVID-19 infection) with late-onset IUGR from 35th week

LIST OF ABBREVIATIONS

AC	Fetal abdominal circumference
ACOG	American College of Obstetricians and Gynecologists
AEDF	Absent end-diastolic flow
AFP	Alpha-fetoprotein
CPR	Cerebroplacental ratio
DV	Ductus venosus
EFW	Estimated fetal weight
FIGO	International Federation of Gynecology and Obstetrics
GA	Gestational age
ISUOG	International Society of Ultrasound in Obstetrics and Gynecology
IUGR	Intrauterine growth restriction
PAPP-A	Pregnancy-associated plasma protein-A
PI	Pulsatility index
PlGF	Placental growth factor
RI	Resistance index
TA	Tibial artery
UA	Umbilical artery
UtA	Uterine artery
WHO	World Health Organization

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INTRODUCTION

Clinical relevance of the study

A high-risk pregnancy is a relatively frequent condition in the population of pregnant women and poses a significant healthcare burden due to a wide spectrum of occurring complications. Moreover, it affects approximately 6-33% of the cases of pregnant women and requires not only additional assistance and specific evaluation, but also treatment and obstetrical intervention. A high-risk pregnancy is defined as an unexpected medical or obstetrical condition associated with a pregnancy affecting the health or well-being of the mother or the fetus and associated with stillbirth [1, 2]. This study focused on pregnant women with multiple or especially worrisome high-risk conditions such as hypertensive disorders, diabetes, intrahepatic cholestasis of pregnancy and the coronavirus disease (COVID-19) that not only tend to trigger vascular disfunction, placental dysfunction, but also may lead to intrauterine growth restriction (IUGR).

Furthermore, since there is no uniform standard consensus, diverse definitions of IUGR have been used by different countries and associations [1, 2, 3, 4]. Unfortunately, so far there has been no treatment available for this fetal condition. Therefore, based on the gestational age at the time of diagnosis, the fetal growth restriction is classified into early-onset IUGR (<32 weeks) and late-onset IUGR (≥32 weeks).

High-risk pregnancy with IUGR is affecting 10-15% pregnancies worldwide [5-7]. Better perinatal outcomes can be associated with the right timing for the detection of high-risk pregnancy, especially impacting IUGR and proper monitoring crucial for perinatal outcomes and normal neurodevelopment of newborns [8].

Moreover, the delivery timing is guided by a serial sonographic surveillance of the fetal growth and well-being, and the maternal condition by balancing the risk of stillbirth with the benefits of advancing gestation [9]. Obviously, traditional prognostic factors such as fundus measurements deployed as one of the follow-up tools in late pregnancy are not sufficient. For better clarification and identification of late-onset IUGR, an additional predictive and prognostic tool like the ultrasound scan in the 3rd trimester needs to be performed. After detecting the condition of high-risk pregnancy, carrying out an intensive monitoring of the fetus lowers the risk of stillbirth. Meanwhile, the screening of maternal factors and biomarkers in the third trimester increases the diagnostics of late hypertensive disorders in pregnancy and may be useful for the evaluation of fetal wellbeing [2,10]. The fetal surveillance

tests carried out in evaluating the fetal condition include uterus fundus measurement, NST/CTG, biophysical profile or modified biophysical profile, ultrasound measurements of the fetal biometry and the Doppler ultrasound measurements of the umbilical artery (UA), the middle cerebral artery (MCA), the uterine arteries (UA) and the ductus venosus (DV) [11–15]. Doppler studies conducted worldwide have revealed that the most frequently used UA Doppler is a proper tool for the identification of an aggravating fetal condition in early-onset IUGR to be used both as a prognostic tool and a marker in stratifying the stable or aggravating fetal condition. A large randomized clinical trial has provided evidence-based management techniques for early-onset growth-restricted fetuses that enable to recognize the abnormal change emerging in the umbilical artery Doppler examination as one of the signs signaling the aggravating fetal condition, however, it is not accurate in late-onset IUGR [16]. Even though late-onset growth-restricted fetuses are frequently associated with a low pulsatility index of the middle cerebral artery, there is no clear evidence or appropriate guidelines to determine the right time of delivery [17,18]. Nevertheless, the same techniques cannot always be relied on in the cases of late-onset IUGR.

Physiologically, the resistance of UA is gradually decreasing during pregnancy [19], as it is known that the UA parameters reflect only the placental blood flow, however, they do not indicate the fetal condition later in pregnancy. More importantly, the increased resistance or the pulsatility index of UA is a marker for placental insufficiency but not for the fetus [19]. Therefore, there are studies showing that to obtain a better evaluation of the fetal condition of late-onset IUGR, it is necessary to perform the Doppler examination of the middle cerebral artery (MCA) and/or cerebroplacental ratio (CPR). Research studies have shown data suggesting that these two indicators have a better response in detecting an abnormal fetal condition [20].

In terms of non-invasive techniques suitable for monitoring late-onset IUGR fetuses such as Doppler ultrasound of diverse arteries, there are still no uniform guidelines or recommendations for obstetric management available. Nevertheless, the changes in particular central arteries, such as the resistance of MCA, correlate with fetal oxygenation. Currently it is known that the lower the resistance is, the greater is the risk of fetal hypoxia, because of the blood flow centralization causing the worsening of the fetal condition [11]. Moreover, the development and validation of the adjustment of optimal Doppler indices have served well for calculating the cerebroplacental ratio (CPR). Thus, in late-onset IUGR, it serves as a more sensitive parameter to target the fetal deteriorating condition rather than MCA or UA separately. CPR is more di-

rected to fetal blood redistribution, although not always widely used. However, a wider application of Doppler examination for investigating fetuses such as the analysis of the peripheral circulation of the fetal arteries has never been introduced or standardized by the international recommendations; only very few studies have researched the diagnostic and prognostic value of the peripheral fetal vessels (i.e., femoral, tibial, pedis arteries) [21–24].

The most unique and significant benefit for perinatal practice and research can be expected from evaluating not only the central but also the peripheral arteries. This opens new perspectives for fetal monitoring by providing more explicitly analyzed full body-based measurements of the parameters of doppler arteries for the diagnosis of fetal hypoxia, fetal prognosis and the prediction of adverse outcomes.

Animal studies on the development of an aggravating fetal condition and the analysis of the changes occurring in the peripheral arteries reveal the patterns of adaptive mechanisms of circulatory changes in the late sheep IUGR cases [17,25–27]. Moreover, several studies on animals [21,28] investigated the peripheral arteries of IUGR fetuses to assess the progression of hypoxia. This opens new prospects for perinatology aiming to meet the needs for accurate guidelines in monitoring late IUGR fetuses. Thus, there is an ongoing open debate as to which of the Doppler parameters in late-onset IUGR cases show either a progressive or a stable fetal condition. Even though the use of ultrasound routinely in the 3rd trimester is not recommended by the 2021 obstetrical guidelines of the International Federation of Obstetricians and Gynecologist FIGO, the use of Doppler ultrasound is a recognized predictive and accurate multiparameter algorithm tool for evaluating the fetal condition in pregnancy. Therefore, Doppler ultrasound examination is performed relatively rarely.

The present dissertation aims to comprehensively describe the importance of ultrasound evaluation regarding the fetal growth and the use of Doppler ultrasound examination of the central and peripheral arteries in high-risk pregnancy fetuses and in late-onset IUGR fetuses and unravel the potential clinical consequences after being diagnosed with the increased resistance of the tibial artery PI. The longitudinal and highly standardized study is expected to provide strong and reliable evidence on the efficiency of monitoring the fetal condition in late-onset IUGR by means of Doppler of the central and peripheral arteries facilitating the evaluation of fetal oxygenation in late-onset IUGR and compromising with variable degrees of hypoxia, distress and loss of full placental sufficiency.

Aim of the study

To evaluate the prognostic value of the fetal tibial artery blood flow pulsatility index Doppler parameters for perinatal outcomes in high-risk pregnant women with and without intrauterine growth restriction.

Objectives of the study

1. To measure and compare the values of Doppler ultrasound pulsatility indices of the fetal tibial artery, middle cerebral artery, umbilical artery and the cerebroplacental ratio in low-risk pregnancies.
2. To measure and compare the values of Doppler ultrasound pulsatility indices of the fetal tibial artery, middle cerebral artery, umbilical artery and the cerebroplacental ratio in high-risk pregnancies (hypertensive disorders, cholestasis of pregnancy, diabetes, COVID-19 infection) without intrauterine growth restriction.
3. To measure and compare the values of Doppler ultrasound pulsatility indices of the fetal tibial artery, middle cerebral artery, umbilical artery and the cerebroplacental ratio in high-risk (hypertensive disorders, cholestasis of pregnancy, diabetes, COVID-19 infection) with intrauterine growth restriction.

Statements to be defended

1. In low-risk pregnancy, the Doppler measurements of the tibial artery pulsatility indices have no prognostic value for perinatal outcomes.
2. In high-risk pregnancy (hypertensive disorders, cholestasis of pregnancy, diabetes, COVID-19 infection) without intrauterine growth restriction, the Doppler measurements of the tibial artery pulsatility indices may have an additional prognostic value for perinatal outcomes in full term pregnancy.
3. In high-risk pregnancy (hypertensive disorders, cholestasis of pregnancy, diabetes, COVID-19 infection) with intrauterine growth restriction, the Doppler measurements of the tibial artery pulsatility indices have a significant additional prognostic value for perinatal outcomes from 35th gestational week.

Scientific novelty of the dissertation

The peripheral fetal blood circulation has not been previously thoroughly evaluated in high-risk pregnancy with and without IUGR. This is a single longitudinal study that involved the analysis of low and high-risk pregnancy from the unique perspective of the impact of the fetal tibial artery Doppler parameters. These measurements were compared with other common antenatal fetal well-being tools, that are recommended in the most recent perinatal guidelines for prediction of perinatal outcomes [22, 23, 29, 30–38].

Therefore, based on clinical data and ultrasound examination, aiming to minimize adverse outcomes associated with pregnancy, the timely termination of pregnancy must be evaluated [29, 39–43]. When suspecting fetal hypoxia, it is important for physicians to determine the optimal time to terminate the pregnancy, therefore, the examination of the peripheral blood vessels would be another new and applicable diagnostic tool which could serve as an additional tool for obstetric management. There has been insufficient research data published on the Doppler parameters of the fetal limbs' arterial velocity (fetal humeral, femoral, tibial and pedis arteries [21, 44–56].

This study is unique in terms of its methodology, the subject of the study, and the focus on the peripheral fetal circulation with a novel model added to the current obstetrical management possibly resulting in better perinatal outcomes. Moreover, the measurements were conducted by a single researcher using the same equipment. Furthermore, unlike other studies, we analyzed both, the pathological and normal values allowing a better interpretation of the results obtained from the subjects of different gestational age and different maternal, fetal backgrounds for fetal surveillance in high-risk pregnancy with IUGR and without IUGR. To the best of our knowledge, this is the first longitudinal study conducted on high-risk pregnancy fetuses with a mean follow-up period of five weeks aiming to identify, compare and analyze the changing patterns of Doppler parameters of the central and peripheral arteries. Also, this study focuses on delineating the clinical features and the best timing for high-risk IUGR fetuses for optimizing the timing of delivery.

1. LITERATURE REVIEW

1.1 Maternal conditions during high-risk pregnancy

According to ACOG, RCOG, NICE, FIGO recommendations, to increase perinatal benefits in the cases of high-risk pregnancy, antenatal fetal surveillance must be started at a certain period and fetal monitoring must be kept until delivery [5, 57-60]. Emphasis must be laid on the fact that our study investigates the fetal adaptation to the maternal conditions during pregnancy that tend to trigger vascular and placental dysfunction and covers pregnancies with and without suspected fetal growth restriction.

Since the study was conducted under the circumstances of the global COVID-19 pandemic, we also included the surveillance of cases affected by the maternal COVID-19 infection. COVID-19 infection has affected the pregnant women's population worldwide and poses a relevant risk for stillbirth which is most dependent on the severity of maternal disease, comorbidities and clinical management during pregnancy [61].

1.2 Hypertensive disorders

A comprehensive study conducted in Norway (n = 2 121 371 women) showed that the prevalence of hypertensive disorders during pregnancy reached 4.7% with the stillbirth rate of 9.2%. According to the latest data of the Lithuanian pregnant women's population, the prevalence of hypertensive disorders is as follows: primary hypertension 5%, gestational hypertension 7% and preeclampsia 2% [62]. The findings of several studies provide evidence regarding a fourfold increase of the risk in the cases of hypertension complicated by preeclampsia [63,64]. In patients with chronic hypertension, the proper medication and control of maternal blood pressure is essential. The effect on the fetus triggered by poorly controlled maternal hypertension or preeclampsia in 60-70 percent of cases may result in the increased risk of fetal growth restriction and worsening of perinatal outcomes [38]. The fetal surveillance must be started from 28-32 gestational weeks on a weekly basis, or more frequently if needed. The optimal clinical decision when to deliver the fetus must be made after a thorough evaluation of the fetal and maternal surveillance data obtained on an individual basis ranging from weekly, twice per week or daily surveillance until delivery [58,60]. The novel biomarkers provide patient-specific risks for preeclampsia and, in combination with maternal factors, can lead to a personalized stratification of the intensity of monitoring for better perinatal outcomes [65].

1.3 Diabetes

According to a study conducted in England (n=2085), women diagnosed with pregestational diabetes disorder are prone to a higher risk for fetal stillbirth, especially after 32 weeks of gestation. The global consensus of obstetricians and endocrinologists claims that women who suffer from pregestational or gestational diabetic disorder controlled with medicines, for their better perinatal outcomes, should be recommended to undergo a fetal surveillance procedure once or twice a week starting from 28-32 gestational weeks (Table 2) [66]. In Lithuania, from 2 to 20 percent of the population of pregnant women have been diagnosed with diabetic disorders, possibly due to the growing body mass index of the population in general. Complications regarding maternal diabetic disorders can affect up to 10 percent of fetuses resulting mostly in fetal macrosomia and diabetic fetopathy, less frequently in IUGR [67].

1.4 Intrahepatic cholestasis of pregnancy

According to the latest findings, intrahepatic cholestasis puts pregnant women at a high risk by affecting approximately 2 percent of pregnancies worldwide [68]. Recent studies have revealed that most of the women diagnosed with intrahepatic cholestasis are residents of Chile and Bolivia, i.e., around 15%, Sweden 3%, Italy 1%, the US 0.01%, and Lithuania – 0.5% [69]. This pregnancy-specific liver disease typically presents in the third trimester and must be managed following the recommendations for fetal surveillance protocols worldwide. As of today, according to the RCOG recommendations, the clinicians should be aware that neither CTG nor fetal ultrasound are able to always predict stillbirth or prevent it in this type of high-risk pregnancy [59]. Researchers are trying to find more accurate tools to predict adverse outcomes in intrahepatic cholestasis of pregnancy, that is why we also included these cases in our research aiming to evaluate the response of fetal peripheral arteries under the maternal cholestasis condition. Therefore, emphasis of our study was laid on the cases with and without IUGR. According to the latest RCOG guidelines of the year 2022, stillbirth risk is higher than background risk if the total bile acids amount to more than 100 micromole/L in 35-36 weeks [Grade A], to 40-99 micromole/L in 38-39 weeks and to 19-39 micromole/L in 40 weeks. Even though the fetal surveillance test can be false negative and not always predicts fetal wellbeing in patients with intrahepatic cholestasis, the ACOG guidelines recommend the antenatal fetal surveillance testing to be carried out once or twice per week. All the guidelines worldwide

agree that the test of the total bile acids must be repeated once a week until the decision regarding the delivery is taken under the findings.

1.5 Coronavirus disease (COVID -19) during pregnancy

Recently published studies have reported that women suffering from coronavirus disease (COVID -19) during pregnancy become high-risk pregnant women with an increased risk of adverse perinatal outcomes [70]. Recently it has been agreed that the risk emerges mostly from the severity of maternal respiratory illness. The latest evidence-based data published by CDC, FIGO and WHO reveals that coronavirus disease (COVID-19) cannot be transmitted to the fetus during pregnancy, therefore, as research studies show, newborns suffer from only mild forms of coronavirus disease (COVID-19). Furthermore, the intrauterine transmission of coronavirus disease (COVID-19) to the fetus is very rare and is possibly due to the low angiotensin-converting enzyme 2 and the transmembrane serine protease 2 needed for the virus entry into the cells of the placenta. The main study (n=342) [71] of the year 2021 showed that COVID-19 associations with adverse perinatal outcomes were related to preterm delivery. Also, cases ranging from a severe form to the critical coronavirus disease (COVID-19) during pregnancy, if compared to mild forms of this infection, are related not only to a stronger likelihood for the intensive care hospitalization, but also to the fetal growth restriction and adverse neonatal outcomes (59,72,73). Thus, when analysing and comparing the fetal surveillance techniques, to disclose the impact of this infection on fetuses' adaptation, we included maternal Covid-19 cases.

1.6 The physiology of a normal fetal growth in the uterus

The fetal size in the uterus is dependent on two principal factors: the duration of pregnancy and the intrauterine growth velocity. The major factor for normal fetal growth is the normal placental function. In healthy pregnancy, which is not interfered with inherited fetal diseases, the fetus will grow up to its genetic potential. In general, the most important factors for a negative impact on the growth are poor maternal nutrition, one or more co-morbidities, infections in early or late pregnancy, pregnancy-related diseases, and medications.

The metabolism between mother and fetus occurs through the placenta. The physiologic development of the placenta follows these steps: at pregnancy week 11, the placenta attaches to the uterine wall, at about 12-13 weeks, the increased blood supply enters the fetus through the spiral arteries, which continues up to 24 weeks of pregnancy reaching 993 ml/min/kg, then at 34 weeks

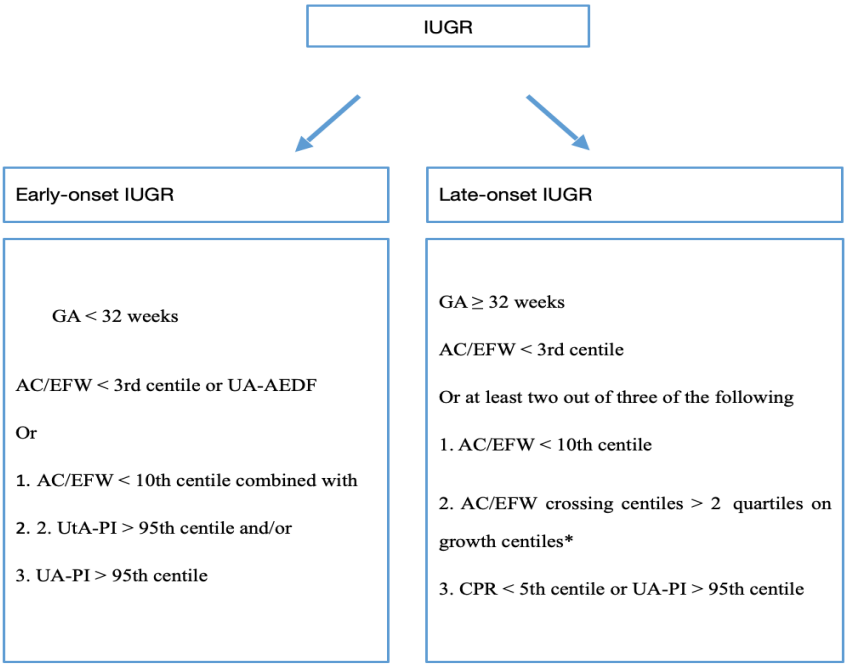
it drops to 360 ml/min/kg, and at 38 weeks when the fetus is term, the blood supply is reduced threefold, to 296 ml/min/kg [74].

1.7 Intrauterine growth restriction (IUGR)

1.7.1 Definition and epidemiology of intrauterine growth restriction (IUGR)

According to "ISUOG Practice Guidelines: diagnosis and management of the small-for-gestational-age fetus and fetal growth restriction" provided by a scientific organisation entitled "The International Society of Ultrasound in Obstetrics and Gynecology", the term of IUGR agrees with the latest Delphi consensus criteria for FGR, IUGR defining the fetus in the absence of congenital anomalies (i) a very small fetus (abdominal circumference (AC) or EFW < 3rd percentile) or (ii) a small fetus (AC or EFW < 10th percentile (according to the Hadlock growth standard)) with additional abnormal Doppler findings or a decrease in AC or EFW by two quartiles or more. It was previously described (ISUOG) as the fetus failing to reach its genetically predetermined growth potential for the given growth charts or (ii) AC or the estimated fetal weight (EFW) below the 3rd percentile – an isolated criterion - at any gestational age [8,75].

According to the timing of the diagnosis of gestational age, IUGR has been classified into two types. Early-onset IUGR is diagnosed at or below 32 weeks of gestation. Late-onset IUGR is the one detected after 32 gestational weeks (Figure 1) [10,76].



**Growth centiles are non-customized centiles. Abbreviations: GA, AC, AEDF, CPR, EFW, GA, PI, UA, UtA. Reproduced from Gordijn et al.*

Figure 1. Definitions for early- and late-onset fetal growth restriction (IUGR)

In terms of a general population of fetuses, late-onset IUGR is a much more prevalent condition compared to early-onset IUGR. This is strongly related to a different etiologic spectrum of the fetal growth impairment between early- and late-onset IUGR, as explained by FIGO (Figure 2).

Early-onset IUGR is easier to detect during a routine ultrasound check up, while late-onset tends to be undetectable more frequently notwithstanding the fact that it is more widespread than early-onset IUGR with a prevalence of 5%–15% compared to early-onset IUGR of the prevalence of 0.5%–1% [77].

1.7.2 Risk factors of intrauterine growth restriction

It is worth pointing out that a simplified classification for the evaluation of IUGR condition is insufficient due to the necessity to understand the difference between a possible etiology and risk factors. The biggest confusion in

most of the literature is between “etiologies” (or pathogenetic pathways) and “risk factors” for IUGR (Figure 3). Furthermore, aiming to explain the terms more explicitly, FIGO provides an example that maternal conditions such as chronic hypertension, kidney diseases, systemic lupus erythematosus, and diabetes should be included in a list of risk factors for IUGR due to a possible abnormal placentation leading to IUGR (Figure 2-4). Unfortunately, in most literature sources, these factors are listed as “maternal etiologies” for IUGR [78].

The research literature defines traditional maternal risk factors that are associated with the IUGR fetus pregnant women. The importance of obstetric history – previous pregnancy affected by IUGR or preeclampsia – appears to be not the only traditional factor.

Moreover, several more medical conditions in women confirmed with IUGR fetuses have been identified:

- Chronic hypertension.
- Chronic kidney disease.
- Systemic lupus erythematosus.
- Inflammatory bowel disease.
- Antiphospholipid syndrome.
- Pregestational diabetes (longstanding).

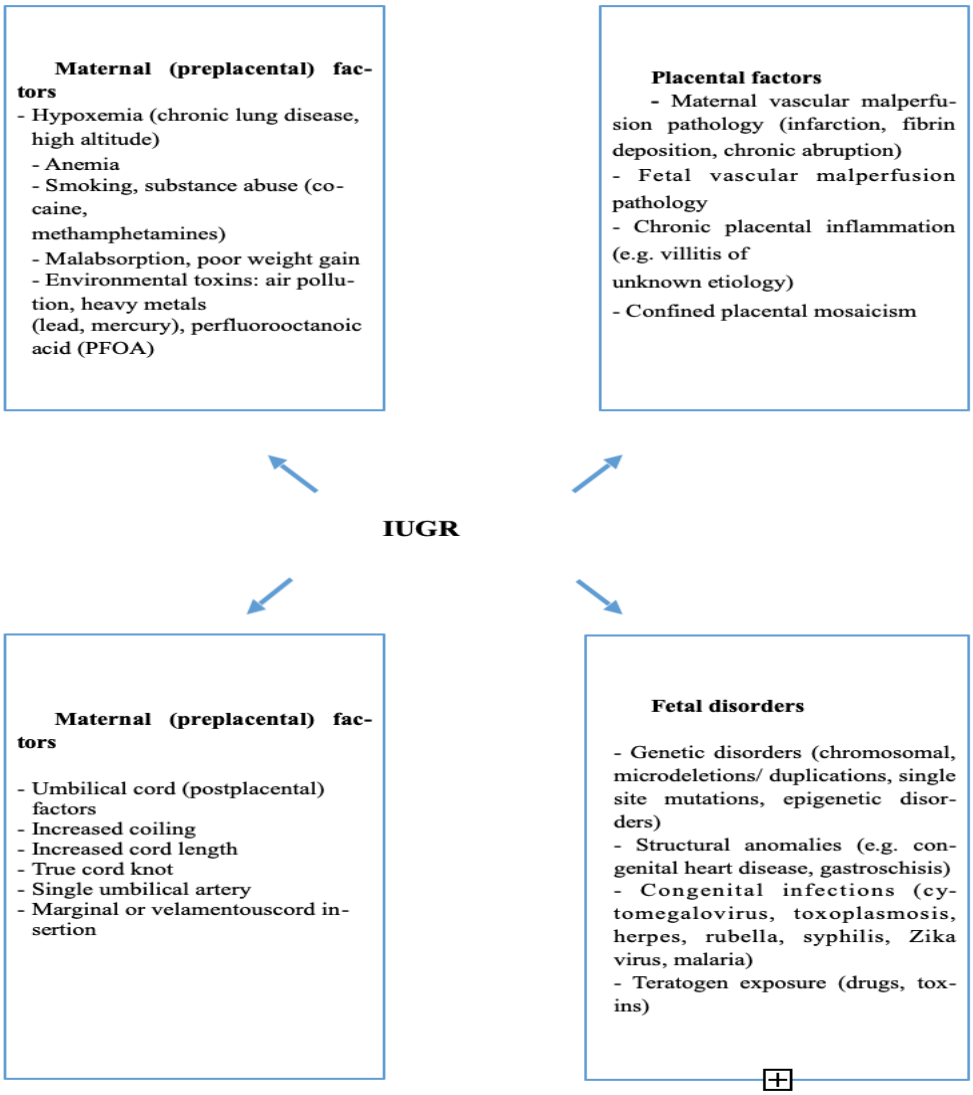
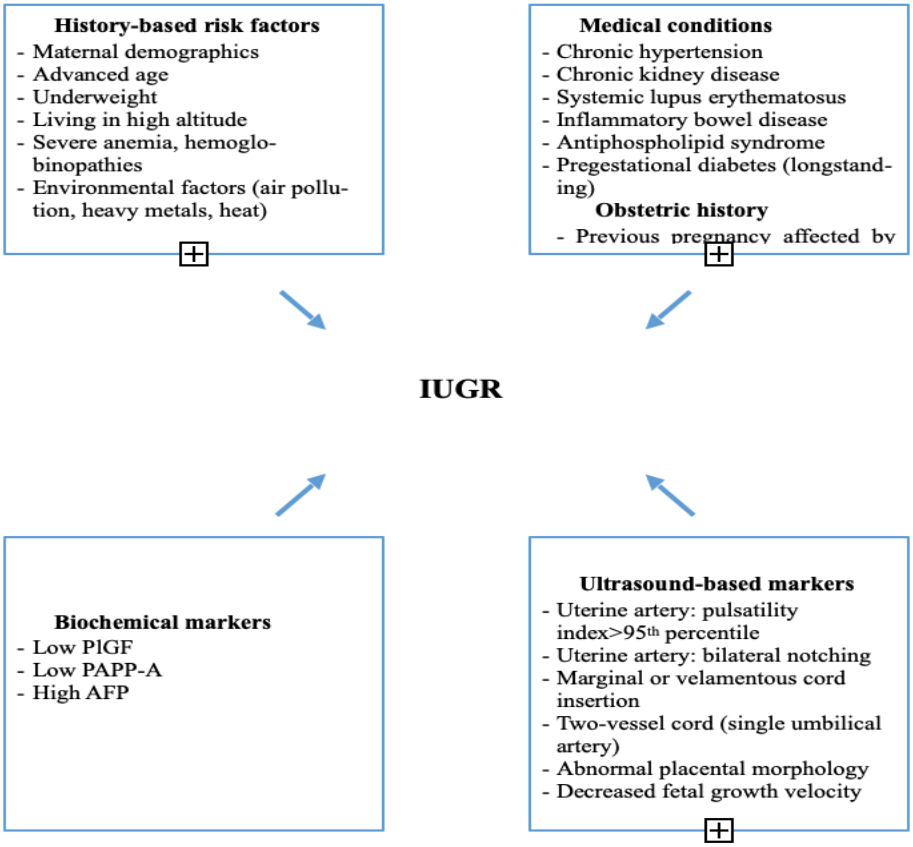


Figure 2. The suboptimal uteroplacental perfusion and fetal nutrition are demonstrated according to FIGO guidelines regarding the common etiologies for the IUGR [78].



Abbreviations: FGR, PlGF, PAPP-A, AFP.

Figure 3. Antenatal and neonatal risks linked to IUGR fetuses are demonstrated according to FIGO [78].

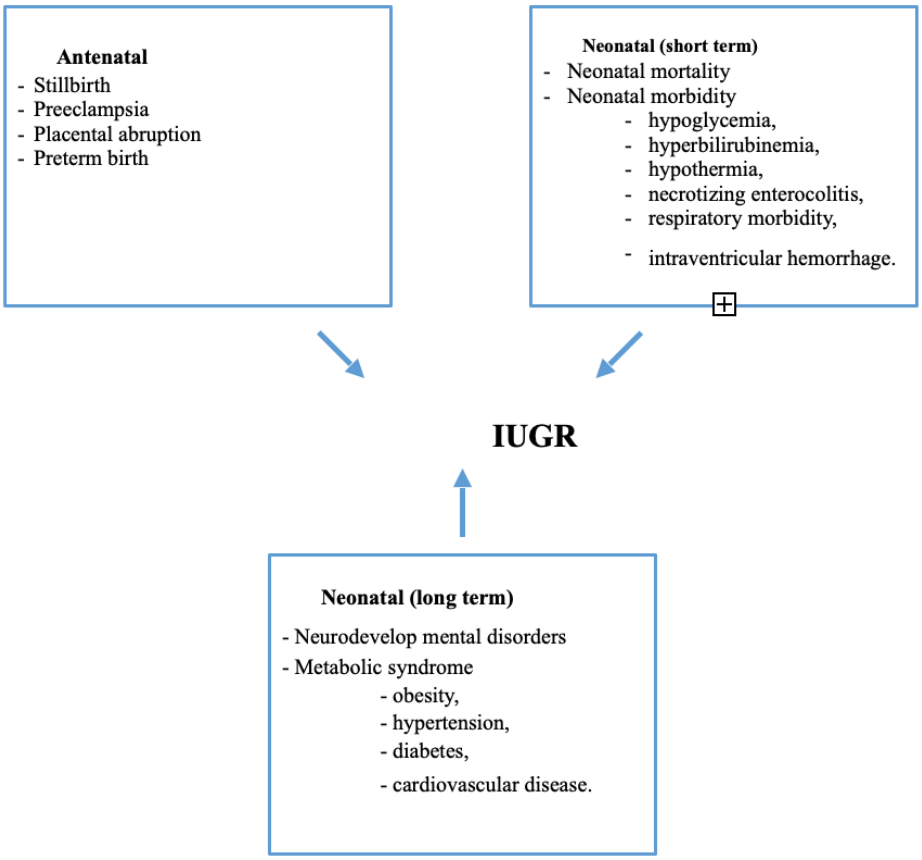


Figure 4. Maternal risk factors for fetal growth restriction are demonstrated according to FIGO [78].

1.7.3 Adaptation of intrauterine growth restriction fetus

Nevertheless, there is also growing evidence of the occurrence of progressive fetal hypoxia and placental functional changes in late-onset IUGR. It generally manifests as the main cause of stillbirth, neonatal mortality, and morbidity in the world [12, 79, 80]. Affected late-onset IUGR fetuses present with a brain-sparing effect, while abnormal Doppler findings show the hemodynamic changes as an adaptation of the fetus to hypoxia [18]. Thus, newborns are associated with a higher risk for adverse outcomes of neurodevelopment.

The umbilical vein through placenta nourishes the fetus with nutrients and oxygenated blood. The blood passes the ductus venosus, one of the three fetal shunts that closes after birth, through the inferior vena cava to the right atrium of the heart. Oxygen-rich blood passes the second shunt, foramen ovale, into the left atrium, then flows into the left ventricle to the aorta, and further to the brain and the systematic circulation. Next, the deoxygenated blood from the fetus passes on through the right atrium and the ventricle to the pulmonary trunk and through the third fetal shunt, ductus arteriosus, and the descending aorta through the two umbilical arteries returns to the placenta.

Depending on the time of pregnancy, the fetus responds to hypoxia in a specific way due to the immaturity of the fetal cardiovascular and other systems [81-83]. Therefore, in late-onset IUGR, the fetus can tolerate the hypoxic state for a shorter period than preterm fetuses. The cardiovascular system of the fetus with chronic hypoxia adapts and gives priority to blood supply to the brain, myocardium, and kidneys [19]. Even though the fetal endocrine, metabolic, cardiovascular systems try to adapt, the fetal demand for nutrients is not fully met, therefore, a high incidence of intrauterine deaths, especially in early-onset IUGR, is likely to occur [17, 18, 84].

Dawes and colleagues [85] were the first researchers to describe the centralization of the fetal blood flow from the periphery to the central organs in the case of sheep fetuses suffering from hypoxia. It was explained as a compensatory mechanism, an adaptation to the changed intrauterine conditions of the fetus. The responses of sheep fetuses to hypoxia differed depending on the time of pregnancy. Peripheral vasoconstriction resulting from sympathetic leakage is usually already regulated in late-onset IUGR fetuses when there is resistance to the effect of vasodilators, such as nitric oxide (NO). The studies showed that the treatment of sheep fetuses with NO synthase inhibitors at base conditions during late-onset IUGR pregnancy induced a general peripheral vasoconstriction and a marked increase in the fetal arterial blood pressure. The fetal life in late-onset pregnancy was balanced by the tone of NO expansion to properly maintain the fetal arterial pressure. Cardiovascular changes, such as bradycardia, hypertension, and femoral vasoconstriction, as well as the metabolic and endocrine changes conducing to fetal survival, were observed in sheep fetuses under hypoxic conditions. Even though the amount of oxygen flow through the heart of the sheep's fetus decreased, the peripheral blood vessels received less blood, the increased blood supply was directed to the vital organs such as the brain [85-88]. Similar changes are likely to occur in human fetuses undergoing intrauterine hypoxia. However, there are very few studies that have examined the human fetal peripheral blood flow under hy-

poxia. The examination of the fetal response to hypoxia by measuring the peripheral vascular blood flow and comparing UA showed a significant increase of PI in the femoral artery (FA), while no changes were observed in UA. This shows that the FA PI reflects the peripheral perfusion [81, 81, 89]. A study of fetuses from 23 to 42 weeks of gestation [20] revealed that in the presence of fetal circulatory disorders, the measurement of the tibial artery PI allows for the detection of circulatory changes. In IUGR fetuses, the elevated a. tibialis PI was detected from 36 weeks [21, 28].

1.8 Antenatal surveillance techniques applied during pregnancy

Antenatal surveillance tests are commonly used techniques (Table 1) to monitor and detect fetal conditions. Historically, they have been used in combination with other monitoring methods resulting in lower fetal morbidity and mortality. In recent times, antenatal surveillance tests are deployed for not only early diagnostics, but also for managing pregnancy-related conditions/issues. Recently published studies have revealed that such tests play a crucial role in the obstetrical care of high-risk pregnancy groups of patients and in the cases of fetal intrauterine growth restriction [90]. Primarily, in high-risk pregnancy when the fetus is under the impact of hypoxia and acidosis, the antenatal surveillance test can help to prevent the fetus from stillbirth. The data shows that the fetus being under these conditions starts to reduce the fetal movements, also the level of the amniotic fluid usually decreases as well as the heart rate may be impacted. Even though antenatal surveillance tests serve as a universally valuable instrument in monitoring high-risk pregnancy, there are quite a few diverse evidence-based recommendations (Figure 5) on its timing and frequency, therefore it may be rather complicated to assure proper fetal surveillance [91].

Table 1. Antenatal fetal surveillance techniques.

Antenatal fetal surveillance techniques		**Clinical use**
NST	Nonstress test	- The NST is based on the premise that the heart rate of a fetus that is not acidotic or neurologically depressed will temporarily accelerate with fetal movement. - Nonstress test results are categorized as reactive or nonreactive.

CTG	Cardiotocography	- The CTG is based on the response of the FHR to uterine contractions. - In the suboptimally oxygenated fetus, the resultant intermittent worsening in oxygenation will, in turn, lead to the FHR pattern of late decelerations.
MPFM	Maternal perception of fetal movement	A decrease in the maternal perception of fetal movement may precede fetal death, in some cases by several days [116].
BBP	Biophysical profile	The BPP consists of an NST combined with four observations made by real-time ultrasonography: - Fetal breathing movements - Fetal movement - Fetal tone - Determination of the amniotic fluid volume [117]
Modified BPP	Modified biophysical profile	The modified BPP combines the NST, as a short-term indicator of fetal acid–base status, with an amniotic fluid volume assessment, as an indicator of long-term placental function [118]
UA-Doppler velocimetry	Umbilical artery Doppler velocimetry	- Doppler ultrasonography is a noninvasive technique used to assess the hemodynamic components of vascular resistance in pregnancies complicated by IUGR. - Umbilical artery Doppler velocimetry has been adapted for use as a technique of fetal surveillance for the growth-restricted fetus, based on the observation that flow velocity waveforms in the umbilical artery of normally growing fetuses differ from those of growth-restricted fetuses. - Currently, there is no evidence that umbilical artery Doppler velocimetry provides information about fetal well-being in the fetus with normal growth [101,112-114,119-123].

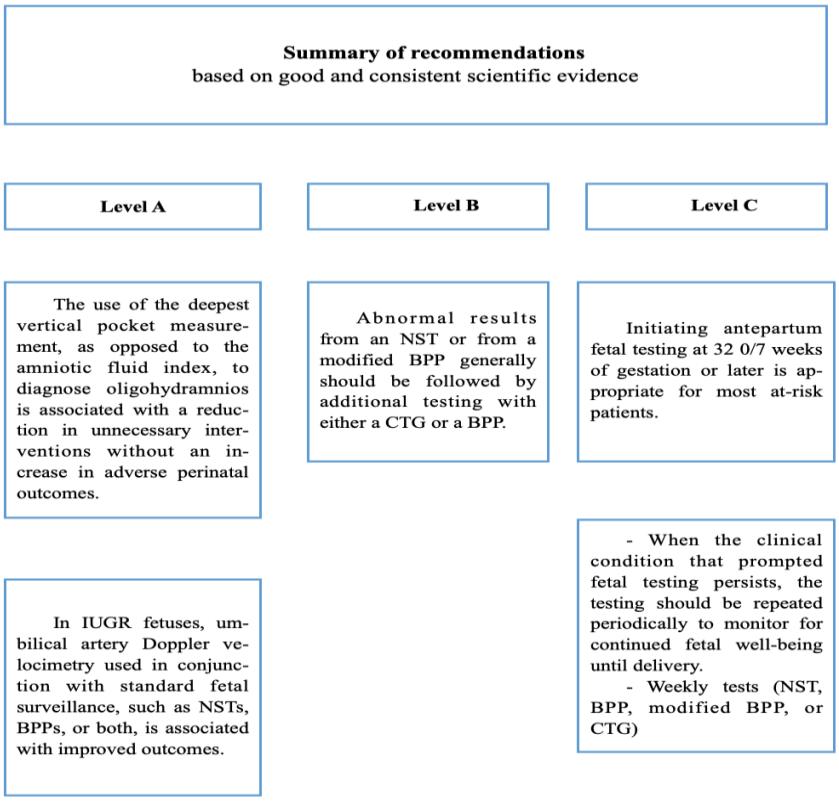


Figure 5. Summary of recommendations based on good and consistent scientific evidence.

1.8.1 Problem of false-negative rate of antenatal surveillance test

Choosing the optimal clinical management in high-risk pregnancy and the appropriate fetal surveillance tool can play a crucial role in obtaining the best fetal perinatal outcomes. There are a couple of aspects to consider in identifying the fetal condition including the false-negative rate of antenatal fetal surveillance tests. Moreover, the relative risk of stillbirth varies because of a consequence of a specific medical condition. The Lancet published the data demonstrating the systematic assessment based on the data retrieved from UNICEF and the WHO. The dataset of 2,833 country-year data points from 171 countries shows a global estimate of almost 14 stillbirths per 1000 births. In contrast to Western Europe and North America, the stillbirth rate in Central Africa is significantly higher [92]. According to the ACOG data, a retrospective cohort study conducted in 2013 revealed the stillbirth rate in “1,000 ongoing pregnancies to be 0.21 at 37 weeks, 0.27 at 38 weeks, 0.35 at 39 weeks,

0.42 at 40 weeks, 0.61 at 41 weeks, and 1.08 at 42 weeks" [57]. Obviously, this data demonstrates that even in high income countries the number of stillbirths is considerably high. This puts consideration on the risk of the false-negative antenatal fetal surveillance test. The studies show that both the NST and CTG alone are more false negative than combined with ultrasound, and both a biophysical profile (BPP) or a modified biophysical profile suggest to be more accurate in detecting deteriorating fetal conditions in high-risk pregnancy or/and in IUGR [57].

1.8.2 Fetal surveillance for high-risk pregnancy

In terms of the standpoint of all the countries worldwide, there is only a matter of the individual approach regarding whether and when to begin antenatal fetal surveillance. The ACOG recommends initiating antenatal fetal surveillance for high-risk pregnancy from 32 weeks. The NICE and RCOG guidelines recommend starting from 28 weeks [93]. In addition, regarding pregnant women who suffer from several high-risk conditions and comorbidities, the surveillance is considered to play a crucial role in terms of perinatal benefits. The global recommendations for when and how frequently to test pregnant women for high-risk conditions are provided in Table 3.

Table 3. Antenatal surveillance recommendations for pregnant women in high-risk pregnancy according to ACOG, FIGO, RCOG.

Factor	Start of Antenatal fetal surveillance	Frequency of antenatal fetal surveillance
Fetal factor		
IUGR		
IUGR + Umbilical artery doppler: - normal - elevated impedance to flow in umbilical artery with diastolic flow present - with normal AFI and no other concurrent maternal or fetal conditions	At diagnosis	Twice weekly or consider hospitalization

	IUGR + Umbilical artery doppler: - absent end-diastolic flow - oligohydramnios - maternal comorbidity [e.g., preeclampsia, chronic hypertension])	At diagnosis	Twice weekly or consider hospitalization
	IUGR + Umbilical artery doppler: - Reversed end-diastolic flow	At diagnosis	Inpatient hospitalization
Maternal factor			
Hypertension, chronic			
	Controlled with medications Poorly controlled	32 0/7 weeks (ACOG) 28 0/7 weeks (RCOG) 27 6/7 weeks (FIGO) At diagnosis	Weekly Individualized
Gestational hypertension/preeclampsia			
	Without severe features With severe features	At diagnosis At diagnosis	Twice weekly Daily
Diabetes			
	Gestational, controlled on medications without other comorbidities Gestational, poorly controlled Pregestational	32 0/7 weeks (ACOG) 28 0/7 weeks (NICE, RCOG)) 32 0/7 weeks 28 0/7 weeks (NICE, RCOG)) 32 0/7 weeks 28 0/7 weeks (NICE, RCOG))	Once or twice weekly Twice weekly Twice weekly
Cholestasis of pregnancy			
	Cholestasis	At diagnosis	Once or twice weekly

Unfortunately, uniform guidelines for the frequency of antenatal fetal surveillance in high-risk pregnancy or in women with comorbidities and/or with/without IUGR have not been provided yet. However, there have been studies highlighting the cases where the maternal medical condition triggered by mother's disease has been assessed as stable under appropriate tests, and the fetal surveillance test was normal with no aggravating condition stated. According to the recommendations of the ACOG Committees, FIGO, RCOG and NICE, the testing of fetal and pregnant women should regularly be repeated at weekly intervals, while the biometry - in 2-3 weeks, unless one of the tests shows a deteriorating fetal status [57].

Several studies have shown that the end of the last trimester is likely to impose the highest risk for stillbirth. For instance, routinely performed antenatal surveillance during low and high-risk pregnancy lowers the risk of stillbirth which tends to increase with the advancing gestational age. Therefore, the low-risk fetal surveillance initiated from 39 gestational weeks may lower stillbirth rate. However, according to the recommendations of antenatal fetal surveillance protocols, the antenatal fetal surveillance of high-risk pregnancy women must be initiated or a delivery induced before 39 weeks. Therefore, in all cases, it should be considered that the risk of fetal stillbirth increases markedly in the last few weeks of pregnancy [94,95].

1.8.3 Biophysical profile

The data regarding the value of a biophysical profile can be found in literature starting from the 1970s. This fetal surveillance technique consists of NST, ultrasound assessment of AFI, fetal breathing movements, total body movements, and limb tone demonstrated by the flexion and extension of the fetal limbs. Later it was compressed to a less time-consuming technique called a modified BPP that only includes NST and AFI. The studies show that a modified BPP can be a more practical tool especially for a routine assessment of fetal well-being in high-risk pregnancy. The modified BPP provides almost as powerful data as the full BPP and is mostly included as part of antenatal testing for high risk maternal and fetal conditions. However, the studies show that BPP has a low positive screen rate and a very low false-positive rate. These data are comparable with nonstress tests, which are reported to have a false-negative rate of 0.19% and a full biophysical profile with a false-negative rate of 0.08% [96-98].

1.8.4 Role of Doppler ultrasound in intrauterine growth restriction management

IUGR is most frequently the result of one or more maternal, placental, or fetal disorders which interfere with the normal mechanisms regulating fetal growth [17,26]. Several ultrasound techniques have appeared to be routinely deployed during pregnancy. This approach includes the uterine artery Doppler, placental morphology, and placental volumes. By means of ultrasound, the abnormal placental morphology is easily defined after measuring the placental dimensions, shape, texture, and cord insertion. In the cases where the placental thickness exceeds 4 cm or is greater than 50% of its placental length, the abnormality of the placental shape is diagnosed, while the placental texture is to be normal when it is homogenous, or abnormal when the placenta is heterogeneous but with multiple echogenic cystic lesions or its appearance is jelly-like with a turbulent uteroplacental flow. Nevertheless, considering their modest predictive accuracy, they should not be recommended to be applied for universal screening for IUGR [99-100].

In most cases early-onset IUGR is first suspected during a routine mid-trimester sonographic assessment of the fetal morphology when the umbilical artery doppler is found abnormal. As opposed to late-onset IUGR, early-onset is much milder and is less commonly associated with preeclampsia. Other possible causes of IUGR can be the changes in the placental form, macro- and microscopic vascular lesions, inflammation, and genetic alterations [76].

Although the surveillance of the fetal condition in the cases of late-onset IUGR in the third trimester is a difficult task, the common practice still tends to follow the Doppler changes in the umbilical artery and ductus venosus while these diagnostic methods are only valuable and reliable in the cases of early-onset IUGR. To determine the optimal balance between the opposing risks of stillbirth and prematurity is a challenging task [125].

1.8.4.1 Doppler ultrasound in early-onset intrauterine growth restriction

Most of the data available from registries of IUGR pregnancies are associated with early-onset IUGR. The TRUFFLE study describing the examination of IUGR up to 32 weeks of gestation and monitoring of DV and cardiotocography (CTG) found that the optimal time for the IUGR fetal birth should be determined according to CTG and early and late venous Doppler monitoring [101]. A comprehensive analysis of the two-year outcomes of the GRIT and TRUFFLE studies concluded that the computerized CTG and ductus venosus

measurements by Doppler were found to be the best observations for early IUGR monitoring [95,96].

1.8.4.2 Doppler ultrasound in late-onset intrauterine growth restriction

In late-onset IUGR, ultrasound findings may show a normal blood flow in the umbilical cord which results in a disguised disease because a normal blood flow recorded in such cases does not directly reflect the fetal condition but is an indicator of the placental blood flow [13,79, 81-83,104]. Even though blood flow in the umbilical cord is found to be normal, the fetus is likely to have already developed a slight centralization of MCA while its CPR is normal. The fetus may already be undergoing nutrient and oxygen deficiency, especially in the peripheral blood vessels [14,105]. Moreover, MCA can be unexpectedly disrupted on average four days before fetal death [105]. Nevertheless, it is still considered to be the most important Doppler examination parameter for monitoring the condition of the fetus [86]. Depending on the time of pregnancy, the fetus responds to hypoxia in a specific way due to the immaturity of the fetal cardiovascular and other systems [87,88].

1.8.4.3 Doppler ultrasound of fetal peripheral arteries

The fetal ultrasound biometry aimed to assess the changes is usually conducted every two weeks, while the fetal Doppler examination can be monitored more frequently, and the changes can be detected more quickly. The researchers who studied the peripheral blood flow of the fetus concluded that the femoral artery blood flow test should not be used to assess the intrauterine fetal status. However, it should be considered that the study was performed on fetuses up to 35 weeks of age, therefore the results obtained should receive critical evaluation [22,24]. Most studies exploring the fetal intrauterine state have been conducted with a scientific focus on the central blood vessels rather than the peripheral ones. There were a few studies describing the response of the peripheral blood vessels to the intrauterine hypoxia in sheep fetuses. Nevertheless, the elevated PIs of the human IUGR fetal tibial artery can be observed from 36 weeks of gestation.

Attention should be paid to the fact that IUGR changes in the human fetal blood flow are more likely to be detected from 35 weeks of gestation when the fetus is turning more mature and approaching the time of the term fetus. Unfortunately, it is also the time for the occurrence of a blood flow rearrangement which interferes with our accurate diagnosis of the fetal condition.

Based on the fetal circulatory changes and adaptation mechanisms in late-onset IUGR, we hypothesize that the peripheral vascular changes (the tibial artery) may more accurately reflect the onset of a deteriorating intrauterine fetal status. This could be one of the signs of an early intrauterine hypoxia in late-onset IUGR fetus, perhaps even an indicator of the right time to the completion of pregnancy, along with other techniques already in use.

1.8.4.4 In search for additional monitoring techniques and clinical guidelines for late-onset intrauterine growth restriction

Moreover, so far there are no uniform guidelines for the use of a feasible tool for the appropriate monitoring of late-onset IUGR.

Taking into consideration the fact that there is no specific treatment for IUGR, a continuous monitoring of the fetal IUGR condition is crucial in terms of timely detection of the changes in the fetal development [11,13–1]. In early IUGR, the circulatory changes typically progress to the venous Doppler changes, whereas in late-onset IUGR, very subtle circulatory changes and the deterioration of biophysical properties may remain unnoticed [24, 106].

A broad range of Doppler studies has reported that the most frequently used UA Doppler cannot be relied on when evaluating the fetal condition in late-onset IUGR, whereas MCA and CPR have shown a better response in detecting an abnormal or only a slightly abnormal fetal condition [124]. It is known that the parameters of UA reflect the placental blood flow but do not reflect the fetal condition. Physiologically, UA resistance is gradually decreasing during pregnancy [13]. An increased resistance or pulsatility index of UA is a marker for placental insufficiency. The resistance of MCA correlates with fetal oxygenation — the lower the resistance is, the greater is the risk of hypoxia, blood flow centralization and worsening of the fetal condition [18]. CPR was serving as a more sensitive parameter to evaluate fetal hypoxia resulting in fetal blood redistribution, rather than MCA or UA separately in late-onset IUGR. However, only very few studies about the diagnostic and prognostic value of peripheral fetal vessels (i.e., tibial artery) are available. The increased resistance of TA-PI in late-onset IUGR as an evaluation of the fetal oxygenation can be compromised with variable degrees of hypoxia, distress and/or loss of full placental sufficiency. The studies on animals reveal similar patterns of adaptive mechanisms of the circulatory changes in late-onset IUGR cases [14,15,107]. Although several studies [11,106] investigated the peripheral arteries of IUGR fetuses to assess the progression of hypoxia, there is still an open debate on which Doppler parameter in late-onset IUGR cases shows a progressive or a stable fetal condition (24).

1.9 Conclusions

Considering that high-risk pregnancy is a risk factor for IUGR, antenatal fetal surveillance in high-risk pregnancy can detect late-onset IUGR. Furthermore, proper antenatal fetal surveillance leads to better perinatal outcomes, less preterm birth complications and a lower stillbirth rate. Unfortunately, there is insufficient data for the best timing and a lack of tools for antenatal fetal surveillance as some of the techniques have false negative results. Nevertheless, the frequency of antenatal fetal surveillance for lowering the stillbirths for any high-risk condition is still not quite clear. In low-risk pregnancy there is no additional value in measuring arteries with Doppler, while adding the peripheral artery Doppler ultrasound in high-risk pregnancy, especially with IUGR, might have a significant additional prognostic value for better perinatal outcomes. To conclude, the observations of the tibial artery PI measurements may assist as an additional tool in the development of guidelines for detecting the deteriorating signs of the fetal condition and in timing of termination, especially for high-risk pregnancy with late IUGR.

2. MATERIALS AND METHODS

2.1 Study design and setting

The prospective observational study was conducted over the period between May 2019 and May 2022 at the Center of Obstetrics and Gynecology of Vilnius University Hospital Santaros Klinikos (VUHSK), Vilnius, Lithuania. In all, 158 pregnant women were invited to participate in the study (Fig.6), all of whom consented to be investigated and signed an informed consent for the participation in the study approved by the Vilnius Regional Biomedical Research Ethics Committee (Vilnius, Lithuania; study approval No. 2019-05-27 No. 2019/5- 1137-624 on May 27, 2019).

The annual childbirth number in VUHSK is approximately 3.000, an average of 800 patients per year are hospitalized in the High-Risk Department. The Obstetrics Day Care unit provides medical services to around 400 patients annually. The most common pathology is false preterm labor (26%), diabetes (10%), hypertensive disorders (9%), cholestasis of pregnancy (6%), hyperemesis gravidarum (7%), patients with Covid-19 infection (1%), with IUGR (4%) patients and other diseases, etc.

The inclusion criteria were as follows:

- Singleton pregnancy.
- Gestational age from 33+0 to 40+0 weeks.
- Maternal age from 18 to 40 years.
- High-risk pregnancy:
  - Hypertensive disorders.
  - Diabetes.
  - Cholestasis of pregnancy.
  - Coronavirus disease (COVID-19).
  - IUGR (EFW<10 percentile).

The exclusion criteria were as follows:

- Twin or multiple pregnancy.
- Small for gestational age fetuses.
- Genetic or chromosomal abnormalities.
- Fetal malformations.
- Withdrawal from the study due to personal reasons.

- Pregnancy <33+0 weeks.

The subjects were divided in three subgroups:

1. Low-risk pregnancy.
2. High-risk pregnancy without IUGR.
3. High-risk pregnancy with IUGR.

The low-risk pregnancy group comprised women with no pathologies, and they consented to participate in the study and followed the uniform surveillance protocol for the high-risk pregnancy study design criteria.

The subjects (n=158) were divided into groups of women with high-risk pregnancy (n=132) and women of low-risk pregnancy (n=26). Considering that the researcher allocated time for visits on Monday mornings, each of these women attended the Obstetrical Day Care Unit for examination procedures for 4 times (n=632 visits). Those followed for high-risk pregnancy were further categorized into study groups of subjects with IUGR (n=62) and without IUGR (n=70) condition. The latter study groups were split into study subgroups by the maternal condition: hypertensive disorder, diabetes, the COVID-19 infection, cholestasis of pregnancy. Unfortunately, 32 participants were excluded from the study: 9 from high-risk pregnancy followed for IUGR, 14 from high-risk pregnancy group without IUGR, 9 from low-risk pregnancy group. The exclusion reasons were as follows: did not meet the study criteria due to additional complications of the pregnancy; were diagnosed with a small gestational age; because of pandemic restrictions in hospital; withdrew from the study voluntarily as demonstrated in the study flow chart (Fig.6).

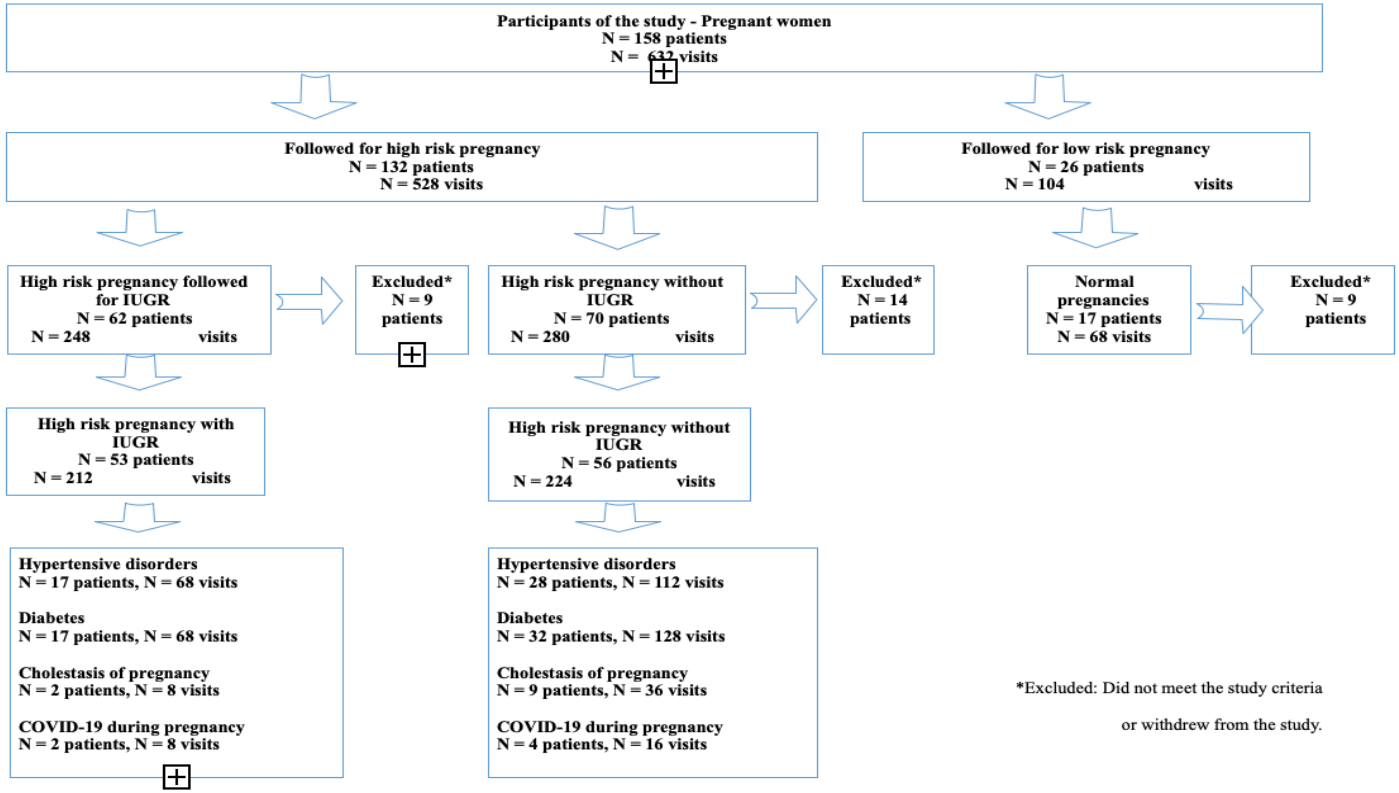


Figure 6. Study flow chart.

During the first visit, the following maternal characteristics data was collected:

- Maternal age.
- Ethnicity.
- Gestational age via the date of the regular menstrual period and/or via the first-trimester ultrasound.
- Previous pregnancies.
- Primary pregnancy risks.
- Comorbidities.
- Current maternal medical conditions.
- Current fetal disorders.

Furthermore, after taking into consideration the maternal and fetal diagnoses, the subjects were investigated by the same single physician on a weekly basis in line with the following procedures:

1. Nonstress test (NST).
2. Ultrasound assessment.
3. Modified biophysical profile.

The study design was as follows (Fig.7):

1. Weekly NST involved attaching sensors fixed by belts to the pregnant participant's abdomen to detect the fetal heart rate acceleration coincident with the fetal movements perceived by the mother. It was performed for 20-30 minutes, until two or more accelerations that peak at 15 bpm or more above baseline, each lasting 15 seconds or more occurred.
2. Modified biophysical profile (modified BPP) on each participant was performed by combining the NST with the amniotic fluid assessment that was performed using ultrasound.
3. Ultrasound assessment was done by a single researcher. The measurements were performed by GE Health Care Voluson S8 by using C1-5 probe, color Doppler to visualize vessels and blood flow.
    a. Biometry measurements were conducted every two weeks.
    b. Doppler measurements were performed weekly.

Ultrasound scanning was performed to measure quantitative and qualitative indicators:

- Biometry was calculated by using Hadlock's automatic equation.
- IUGR was defined as an EFW and /or AC<10^{th} percentile.
- Amniotic fluid index (AFI).

- Doppler waveform pulsatility indices (PI) of the middle cerebral artery (MCA).
- Doppler waveform pulsatility indices (PI) of the umbilical artery (UA).
- Doppler waveform pulsatility indices (PI) of the tibial artery (TA).
- Calculation of the cerebral-placental ratio (CPR): dividing the middle cerebral artery (MCA-PI) by the umbilical artery (UA-PI)

According to the measurements of TA-PI, the participants of high-risk pregnancy groups with the diagnosis of IUGR and without IUGR were divided into two subgroups: a subgroup with normal findings of TA-PI >5 and <95 percentile, and a subgroup with abnormal TA-PI findings >95 percentile.

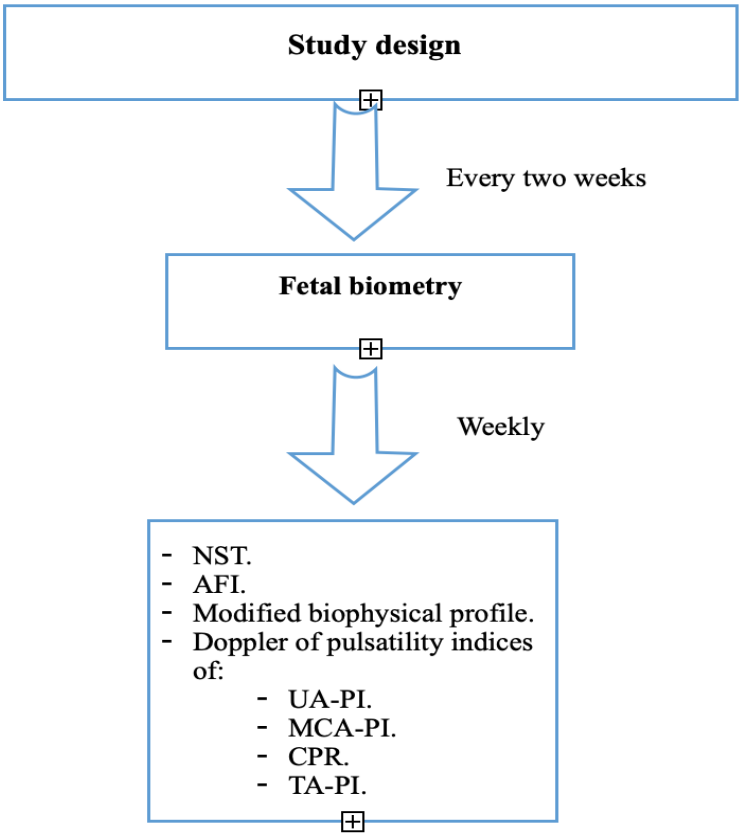


Figure 7. Study design.

Furthermore, weekly Doppler signals from the arteries under analysis were obtained as follows: the insonation angle was focused below 30 degrees to record the umbilical artery (UA-PI) Doppler signals from the free-floating segment of the umbilical cord (Fig. 8). The volume of each sample was located so that it covered the artery lumen, aiming to avoid the adjacent umbilical vein. The fetal MCA was focused on the transverse view of the scull of the fetus so that Doppler signals were obtained from the MCA which was located nearest to the transducer. The sample volume of spectral Doppler was focused in the proximal third of the MCA, near its origin site in the circle of Willis (Fig.9). The insonation angle was as near 0 degree as possible. Undue pressure was escaped for ultrasound transducer.

Furthermore, the cerebral-placental ratio (CPR) was calculated after the data had been collected. It was calculated by dividing the MCA Doppler flow by the umbilical artery UA Doppler flow.

The core focus of this study was to obtain accurate measurements of the peripheral tibial artery (TA) (Fig.10). The methodology involved the following steps: first, we applied the Doppler technique on the site of the lower extremity of the fetus where the tibial and fibular bones were clearly visible. Secondly, the angle between the transducer and the bones was adjusted to 45° or less. Next, the color Doppler gate was placed over the vessel in the leg between the two bones to locate the anterior TA (Fig.11). For more accurate measurements, the Doppler wave form indices were measured manually, because the automatic calculations have not been installed in the Voluson E8 machine (Fig.12).

Emphasis should be laid that our study focuses on the parameters of the pulsatility index (PI) of the measured arteries. The pulsatility index is a concept that defines the difference between the peak systolic flow and the minimum diastolic flow velocity which is divided by the mean velocity recorded throughout the cardiac cycle. We were able to measure the velocity of TA in all fetuses, signals were recorded for at least 5-6 cycles with an equal shape and an amplitude of the blood flow waveforms. The PI of the anterior tibial artery was compared with the TA-PI standards published by Kurmanavičius and Wisser et al. [19, the standards for tibial artery PI percentile are presented in Annex 1].

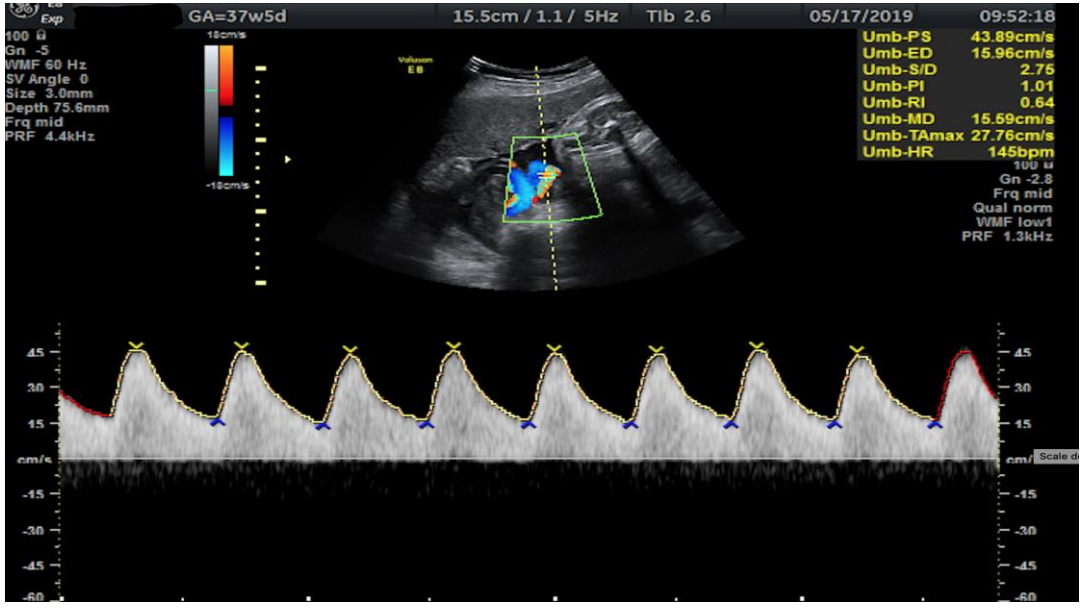


Figure 8. Doppler examination demonstrates the technique of automatic measurement of the blood flow of the umbilical artery. The measurement was taken at 37+5 weeks.

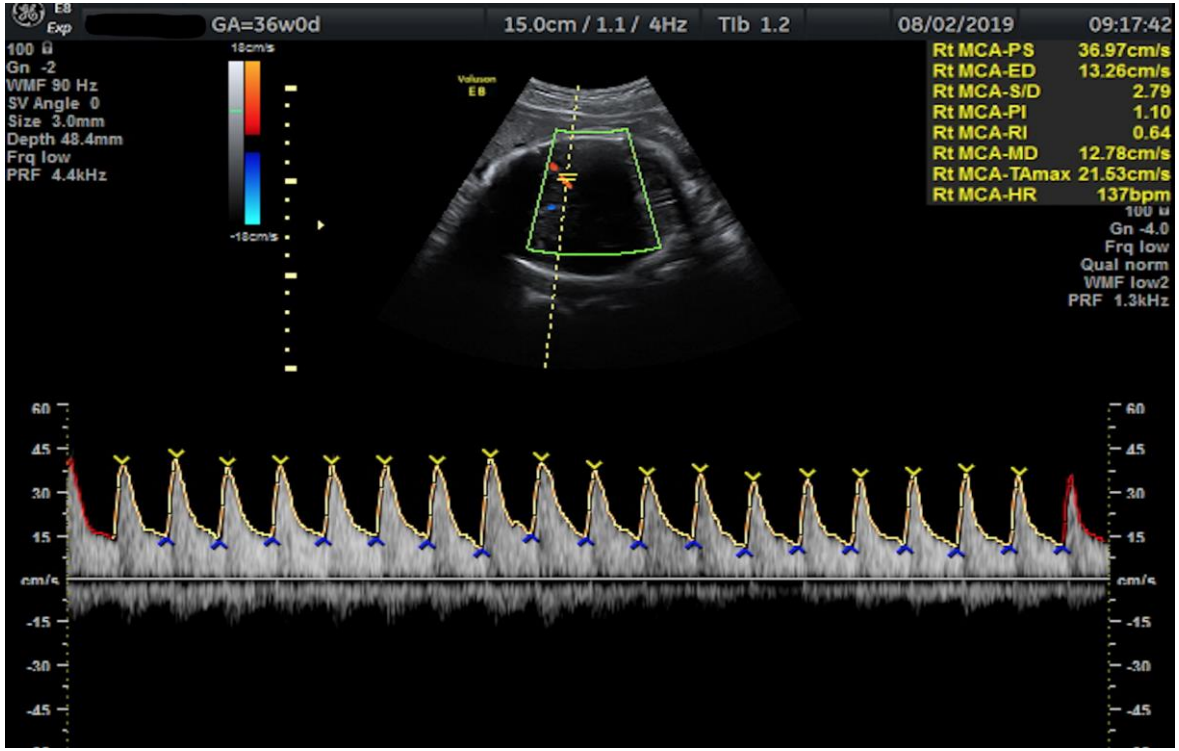


Figure 9. Doppler examination demonstrates the technique of the measurement of the blood flow of the middle cerebral artery. The measurement was taken at 36+0 weeks fetus with IUGR.

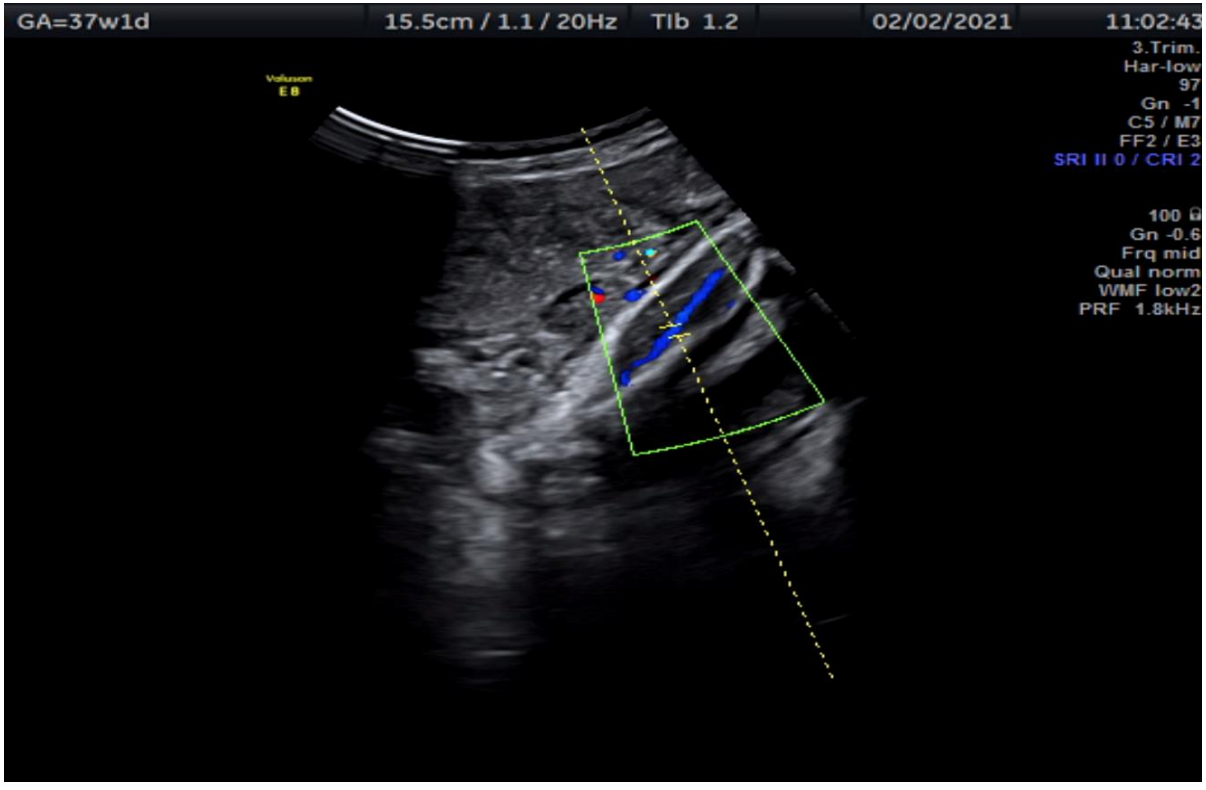


Figure 10. Doppler examination demonstrates the technique of measurement of the blood flow of the fetal tibial artery. The measurement was taken at 37+1 weeks.

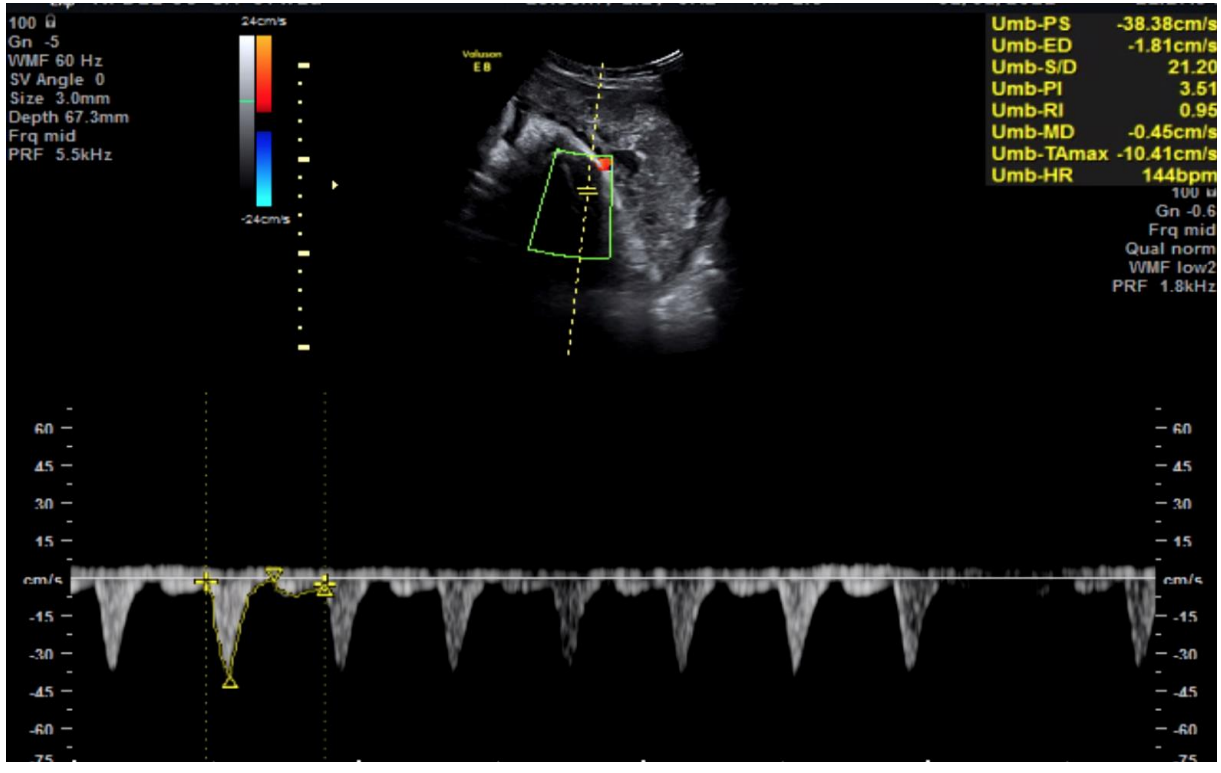


Figure 11. Doppler examination manual measurement technique for the fetal tibial artery at 36+5 weeks demonstrates normal TA-PI.

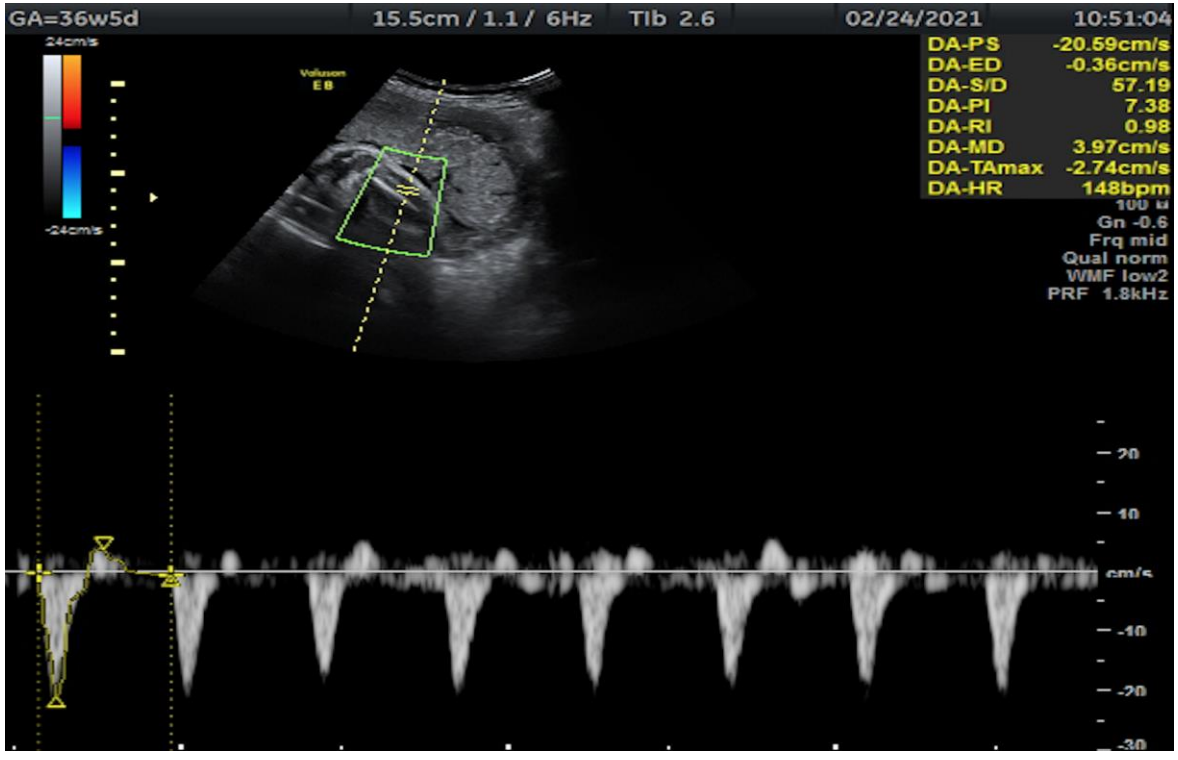


Figure 12. Doppler examination manual measurement technique for the fetal tibial artery at 36+5 weeks demonstrates the reverse flow of abnormal TA-PI (PI>95th percentile).

The information about mothers and newborns was obtained from the internal database of Vilnius University Hospital Santaros Klinikos:

- Mode of delivery: spontaneous vaginal delivery, instrumental delivery, or Cesarean section.
- Amniotic fluid color.
- Gestational age.
- Gender.
- Birth weight.
- Neonatal 5 minute - Apgar scores.
- Laboratory data: umbilical cord pH values.
- Neonatal outcomes:
  - Need for respiratory support.
  - Neonatal jaundice.
  - Neonatal hypoglycemia.

2.2 Statistical methods

The calculations of the study sample size were performed to determine the number of participants needed to detect clinically significant data of parameters. Our sample size of 126 subjects is considered sufficient to derive reliable sufficient estimates from all the performed statistical tests. The data was validated by using the standardized data validation plan to avoid including patients with missing data or data that falls outside the predefined plausibility ranges.

The collected data wasa stored in the database. The statistical analysis of this data was performed by applying the program package SPSS 27.0 (Statistical Package for the Social Sciences). While analyzing the quantitative data, the main characteristics of their distribution were evaluated: mean (V), standard deviation (SD), median [25-75%], the interquartile range (IQR), degree of freedom (df). The number of cases (n) and distribution by percentage of ranking variables are presented. Kolmogorov-Smirnov test was used to test the hypotheses regarding the normality of the distribution of parameters. Quantitative values of the normal distribution were compared using parametric criteria, while ordinal variables and non-normally distributed quantitative values were estimated by non-parametric tests. The chosen level of confidence was 95%, and the level of significance was p=0.05. The test results were considered statistically significant if $p<=0.05$, with a trend towards significance

>=0.05, but <0.1. The comparison of independent samples was carried out by means of the parametric analysis of variance (ANOVA) or the non-parametric Dunn's Kruskal-Wallis test. Meanwhile, the multiple comparison of samples was conducted by applying the Dunn's Kruskal-Wallis test for pairwise comparisons. The Chi-square ($\chi 2$) criterion was used to assess the interdependence between the nominal scale and the tabulated frequency characteristics. Fisher's exact or Monte Carlo (for small samples) and the asymptotic $\chi 2$ test were used depending on the sample size.

All Doppler examination parameters were transformed into *Z*-values according to normative references (105,108).

The estimated fetal weight was calculated using Hadlock's equation formula C introduced by Hadlock et al, calculated automatically with the GE Healthcare Voluson E8 system:

- Log(10) BW = 1.335 - 0.0034(abdominal circumference [AC])(femur length [FL]) + 0.0316(biparietal diameter) + 0.0457(AC) + 0.1623(FL);

The regression equations of the 5th and 95th centiles were determined as follows: UA PI (79), CPR (109), MCA PI (116), TA (28). The following formulas:

The Doppler examination parameters of the tibial artery pulsatility indexD were transformed into *Z*-values according to:

5P:10**((1.006-0.003034*x+0.00007539*x**2)-
((0.015+0.0003455*x)*1.253*1.645))-6.176;

50P:10**(1.006-0.003034*x+0.00007539*x**2)-6.176;

95P:10**((1.006-0.003034*x+0.00007539*x**2)+((0.015+0.0003455*x)*
1.253*1.645))-6.176.

The Doppler examination parameters of the middle cerebral artery pulsatility index were transformed into *Z*-values according to:

5P: -0.000132 *(x*x*x) + 0.005824 *(x*x) + 0.012206 *x - 0.434344;

50P: -0.000154 *(x*x*x) + 0.006150 *(x*x) + 0.051486 *x - 0.784632;

95P: -0.000184 *(x*x*x) + 0.006864 *(x*x) + 0.093193 *x - 1.106259.

The Doppler examination parameters of the umbilical artery pulsatility index were transformed into *Z*-values according to the following references:

5P: exp(1.5075-0.2843*(x**0.5) - 1.645*(0.0667+0.00398*(x)-0.0276*(x**0.5))**0.5);

50P: exp(1.5075-0.2843*(x**0.5));

95P: exp(1.5075-0.2843*(x**0.5) + 1.645*(0.0667+0.00398*(x)-0.0276*(x**0.5))**0.5).

The Doppler examination parameters of the cerebroplacental ratio (MCA-PI/UA-PI=CPR) were transformed into *Z*-values according to the following references:

5P: -0.000260*(x*x*x) + 0.017328*(x*x) - 0.296292*x + 1.878124;

50P: -0.000288*(x*x*x) + 0.018654*(x*x) - 0.287704*x + 1.885518;

95P: -0.000320*(x*x*x) + 0.020445*(x*x) - 0.293823*x + 2.227013.

The endpoint in the changes of longitudinal values was defined as an abnormal Doppler value (MCA-PI and CPR <5th centile, UA-PI and TA-PI>95th centile). The McNemar test was used to compare the paired group proportions.

3. RESULTS

3.1 General characteristics of study participants, fetal surveillance techniques and perinatal outcomes

In all, out of 158 patients who were enrolled into the study, 126 patients with a total of 504 visits satisfied the eligibility criteria for the present study, as described in the methods section, while 32 were excluded from the analysis. All the participants were Caucasian women of the mean age of 32.5 [29.0-35.3] years (Table 4.)

Table 4. Characteristics of the participants. The IQR - interquartile range, df-degree of freedom, a p value by independent-samples Kruskal-Wallis's test (Pairwise Comparisons of Group by Dunn's test) b p value by Chi-Square tests.

Characteristics	**Group**				**p-value**
	All participants (n=126)	High-risk pregnancy without IUGR (n=56)	High- risk pregnancy with IUGR (n=53)	Low-risk pregnancy (n=17)	
Maternal age, years Median [IQR]	32.5 [29.0-35.3]	33.0 [30.0-36.0] *	33.0 30.0-36.0] **	30.0 [28.0-31.0]*,**	*,**p<0.05
Parity n (%)					
Multiparous	66 (52.4)	33 (58.9)	26 (49.1)	7 (41.2)	p=0.358
Nulliparous	60 (48)	22 (39)	27 (51)	10 (59)	p=0.358
Pregnancy disorders and comorbidities, n(%)					
Preeclampsia	20 (16.8)	11 (19.6)	9 (19.6)	0 (0)	p=0.135
Gestational hypertension	15 (11.9)	9 (16.1)	6 (11.3)	0 (0)	p=0.207
Pregestational hypertension	10 (7.9)	8 (14.3)	2 (3.8)	0 (0)	p=0.067
Coronavirus disease (COVID -19)	5 (4.0)	4 (7.1)	1 (1.9)	0 (0)	p=0.352

Diabetes	4 (3.2)	3 (5.4)	1 (1.9)	0 (0)	>0.999
Gestational diabetes	45 (35.7)	29 (51.8)	16 (30.2)	0 (0)	p=0.242
Cholestasis of pregnancy	11 (19.9)	9 (16.1)	2 (3.8)	0 (0)	>0.999

When comparing the groups of patients by pregnancy risk, the median of maternal age [IQR] of high-risk pregnancy group without IUGR and with IUGR did not differ ($p>0.05$), while in low-risk group, the median age was statistically lower ($p<0.05$). In terms of maternal age, the groups of high-risk pregnancy with IUGR and high-risk pregnancy without IUGR were significantly non-homogenous compared with low-risk pregnancy group (Table 4).

Obviously, high-risk pregnancy groups were significantly older by age. However, no statistically significant differences were observed between the multiparous subjects of these three groups ($p>0.5$). No associations were found between the types of comorbidities among the groups under analysis.

Also, there were no statistically significant associations between the abnormal modified biophysical profile, oligohydramnios, polyhydramnios or nonreactive NST (Table 5).

Table 5. Antepartum fetal surveillance.

Characteristics	**Groups**				
	All participants n=126 (n,(%))	**High-risk pregnancy without IUGR group n=56 (n,(%))**	**High- risk pregnancy with IUGR group n=53 (n,(%))**	**Low-risk pregnancy group n=17 (n,(%))**	**P-value**
Olygohidramnion	4 (3,2)	2 (3,6)	3 (3,8)	0 (0)	p=1,0
Polihydramnion	3 (2,4)	3 (5,4)	0 (0%)	0 (0%)	p=0,203
Non-reactive NST	0 (0)	0 (0)	0 (0)	0 (0)	-

Furthermore, meconium in the amniotic fluid and meconium aspiration syndrome proportions in all the three groups did not differ significantly. Although the differences were found in neonate gender among the three groups, conversely, in the birthweight category, statistically significant differences were seen in all groups ($p<0.05$) with the lowest birthweight of 2371.7 (409.2)

grams in high-risk with IUGR group. Moreover, high-risk with IUGR group comprised newborns of the estimated fetal weight of <5 percentile and <10 percentile. Next, Apgar score at 5 min was significantly lower in high-risk with IUGR group, 9.5 [9.0-10.0] compared to high-risk without IUGR group, 10.0 [9.0-10.0] and low-risk group 10.0 [10.0-10.0] ($p<0.028$). Furthermore, only 0.8% of the study population was diagnosed with metabolic acidosis as their pH of the umbilical cord was below 7. However, the pH of the umbilical artery differed significantly between the groups.

3.2 Low-risk pregnancy group

Our low-risk pregnancy group showed normal pulsatility index in the fetal tibial artery (TA-PI) in all the patients from 33 to 40 weeks. The figure below demonstrates normal parameters of TA-PI at 39+0 weeks (Fig. 13, Fig. 14). Overall, the results of the participants included in low-risk pregnancy group showed normal ranges in the measured vessels, there were no statistically significant adverse perinatal outcomes in newborns (Table 5). The delivery mode of the subjects comprising low-risk pregnancy group was spontaneous labor with no cases of labor induction. However, one labor was completed via cesarean section due to the occurrence of fetal hypoxia during labor.

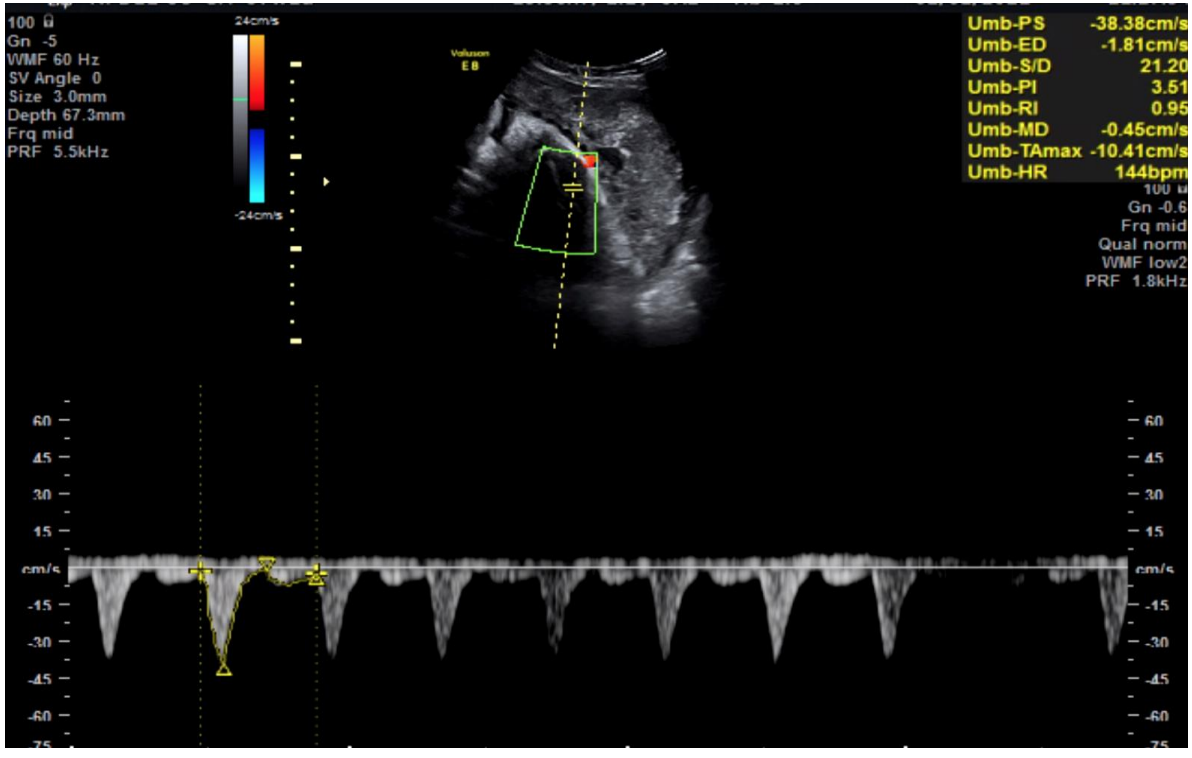


Figure 13. Doppler measurement at 39+0 weeks of normal TA-PI (measured manually).

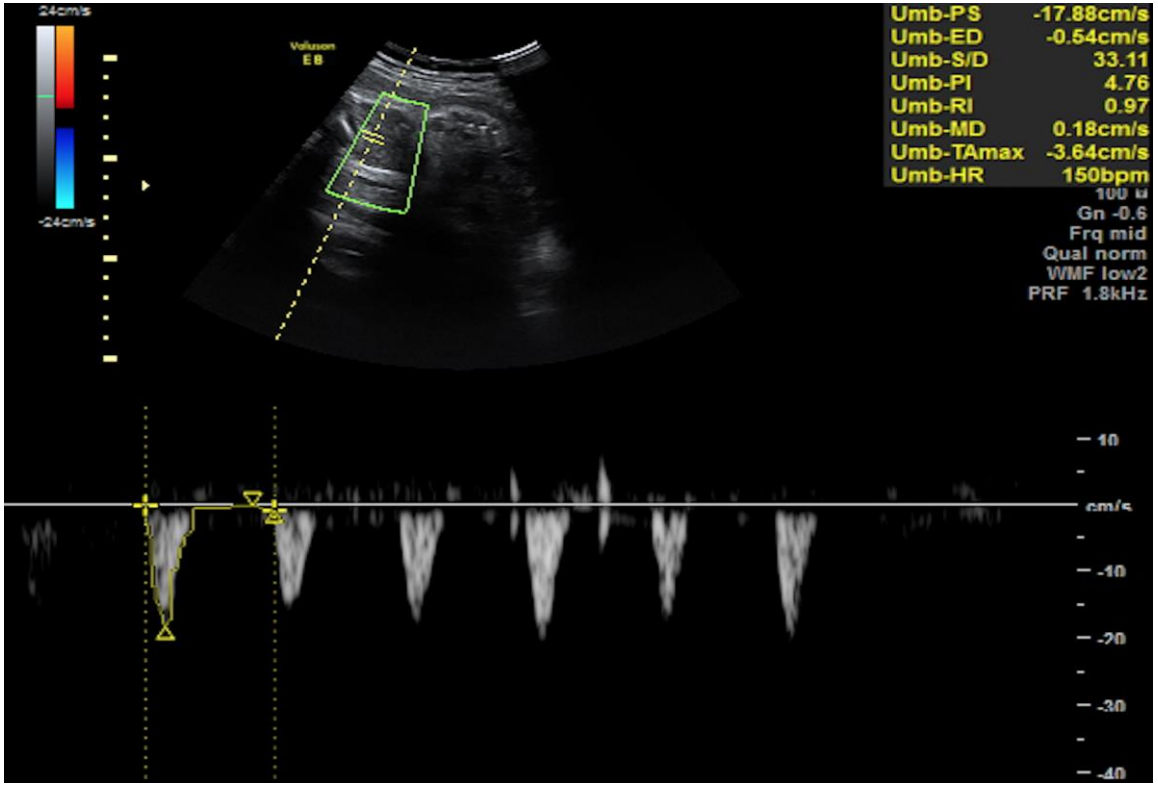


Figure 14. Doppler measurement at 39+0 weeks of normal TA-PI (measured manually).

As indicated in Fig. 15, the Doppler parameters of PI and CPR of all the arteries under analysis were transformed into Z values, according to normative references. As a result, the parameters of the fetal tibial artery remained within the normal range from 33rd until 40th gestational weeks. Furthermore, Z values of the CPR, UA and MCA also remained within normal ranges.

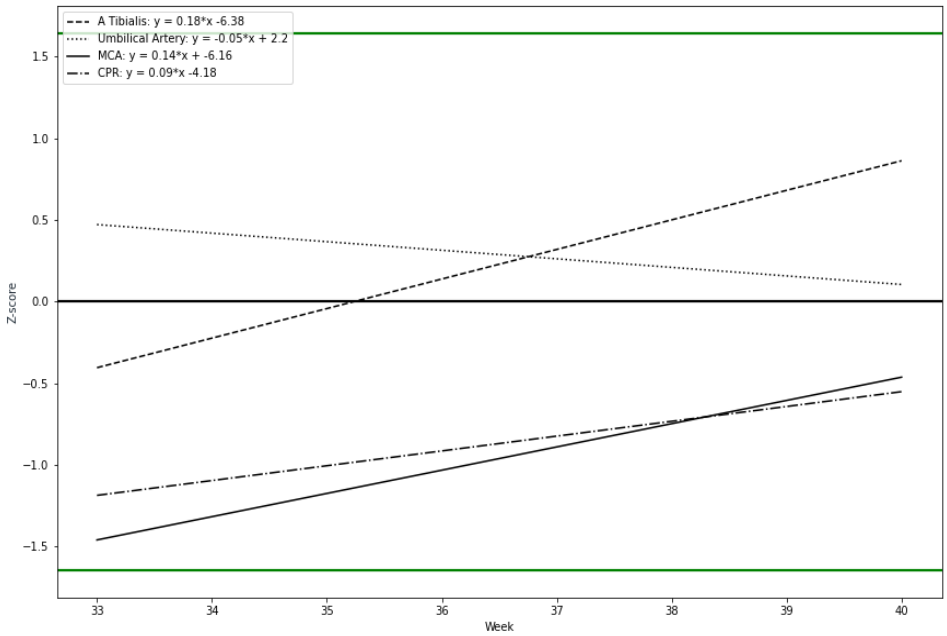


Figure 15. Normal pregnancy longitudinal trends of Doppler parameters in Z-values during the study period: Tibial artery (TA-PI), cerebroplacental ratio (CPR), middle cerebral artery (MCA-PI), umbilical artery (UA-PI).

3.3 High-risk pregnancy without intrauterine growth restriction group

Our analysis of high-risk pregnancy without IUGR group involved the comparison of the fetal surveillance tools with the tibial artery Doppler parameters. The results showed that the comparison of normal and abnormal PI values of the tibial artery with the surveillance tools in high-risk pregnancy without IUGR group showed no statistically significant results (Table 6). Additionally, Doppler parameters of PI and CPR of all the arteries under analysis were transformed into Z values, according to normative references. As a result, as demonstrated in Fig.16, parameters of the fetal tibial artery deviated

most significantly from the norm from 39-40th gestational week and a significant abnormal increase was observed. Meanwhile, Z values of the CPR, UA and MCA remained within normal ranges.

It is worth pointing out that according to our study findings, the tibial artery parameters were the most significantly changing alongside the growing gestational age.

Table 6. Comparison of high-risk pregnancy disorders and maternal comorbidities with normal (TA-PI >5 and <95 percentile) and abnormal (>95 percentile) PI values of the tibial artery during last week before delivery in high-risk pregnancy without IUGR group by using statistical tests (*Pearson's Chi-squared test, ±Fisher's exact test)

Characteristics	Groups			p-value
	Overall, N = 56	TA PI >95 percentile, N =33	TA PI >5 and <95 percentile, N = 23	
Primary arterial hypertension*	8 (14.3%)	4 (17.4%)	4 (12.1%)	0.704
Gestational hypertension*	9 (16.1%)	3 (13.0%)	6 (18.2%)	0.723
Diabetes*	3 (5.4%)	2 (8.7%)	1 (3.0%)	0.562
Gestational diabetes*	29 (51.8%)	12 (52.2%)	17 (51.5%)	0.961
Cholestasis of pregnancy±	9 (16.1%)	0 (0%)	9 (27.3%)	0.007
Preeclampsia±	11 (19.6%)	5 (21.7%)	6 (18.2%)	0.746
Maternal COVID-19 virus±	4 (7.1%)	3 (13.0%)	1 (3.0%)	0.295

Nevertheless, many researchers indicate that CPR is a reliable indicator for evaluating the fetal condition, while MCA as a single indicator is not. This trend is not visible in this group of subjects of our study, either (Fig.16). These results may have been influenced by the fact that our study involved four different pathologies.

3.4 High-risk pregnancy with intrauterine growth restriction group

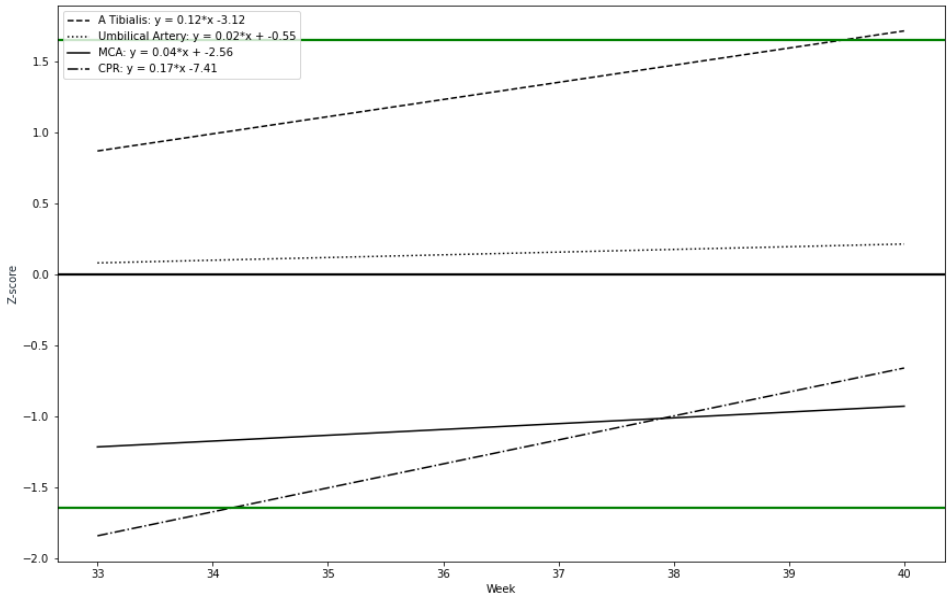


Figure 16. High-risk pregnancy without IUGR. Longitudinal trends of Doppler parameters in Z-values during the study period: Tibial artery (TA-PI), cerebroplacental ratio (CPR), middle cerebral artery (MCA-PI), umbilical artery (UA-PI).

High-risk pregnancy with IUGR group comprised 53 women diagnosed with IUGR who were compared according to normal and abnormal PI values of the tibial artery. The comparison of normal and abnormal PI values of the tibial artery obtained one week before delivery with the surveillance tools in high-risk pregnancy with IUGR group showed no statistically significant results (Table 7). All the women had normal NST, no polyhydramnios was found in any of the groups. In the cases with preeclampsia, the values of the tibialis artery showed a trend towards significance $p<0.1$ (Table 7).

Table 7. Comparison of high-risk pregnancy disorders and maternal co-morbidities (number and percentage) with normal (TA-PI >5 and <95 percentile) and abnormal (>95 percentile) PI values of the tibial artery obtained one week before delivery in high-risk pregnancy with IUGR group by using statistical tests (* Fisher's exact test)

Characteristics	**Groups**			**p-value**
	Overall, N = 53 (%)	**TA PI >95 percentile, N = 41 (%)**	**TA-PI >5 and <95 percentile), N = 12 (%)**	
Primary arterial hypertension*	2 (3.8%)	2 (4.9%)	0 (0%)	>0.999
Gestational hypertension*	6 (11.3%)	6 (14.6%)	0 (0%)	0.317
Diabetes*	1 (1.9%)	0 (0%)	1 (8.3%)	0.226
Gestational diabetes*	16 (30.2%)	14 (34.1%)	2 (16.7%)	0.307
Cholestasis of pregnancy*	2 (3.8%)	2 (4.9%)	0 (0%)	>0.999
Preeclampsia*	9 (17.0%)	9 (22.0%)	0 (0%)	**0.100**
COVID-19 virus*	1 (1.9%)	1 (2.4%)	0 (0%)	>0.999

Additionally, to have a clearer view, Doppler parameters of PI and CPR of all the arteries under analysis were transformed into Z values, according to normative references. As a result, as demonstrated in Fig.17, the parameters of the fetal tibial artery deviated most significantly from the norm at 34-35th gestational week and showed a significant abnormal rise. Moreover, Z scores of CPR were also slightly deviating from the normal range, but not as significantly as those of the tibial artery. Also, Z values of MCA were gradually declining in line with the growing gestational age. The MCA parameters in our study reached a pathological value only at 39-40th gestational week. Meanwhile, the parameters of the UA artery under our analysis remained within the normal range. Our findings show that UA did not have any prognostic value as it remained within normal range. This finding coincides with the results obtained by other authors who claim that umbilical artery Doppler parameters values are not a sufficient prognostic indicator to fetal wellbeing in late IUGR fetuses.

Our analysis showed that the parameters of the tibial artery were changing the most significantly with growing gestational age. Nevertheless, there is not sufficient research to support our findings. Many researchers indicate that CPR is a reliable indicator for evaluating the fetal condition, while MCA as a single indicator is not. This trend is also visible in our study (Fig. 17).

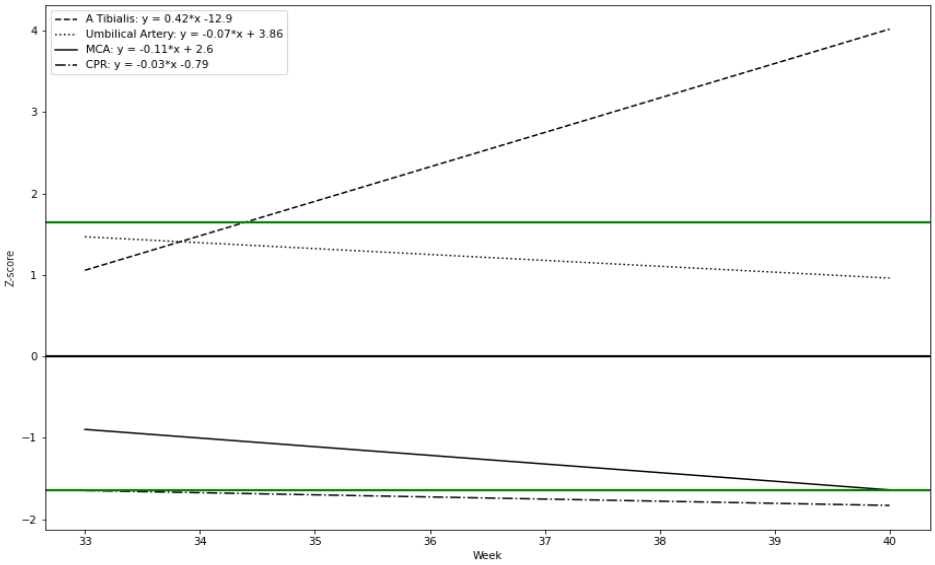


Figure 17. High-risk pregnancy with IUGR group. Longitudinal trends of Doppler parameters in Z-values during the study period: Tibial artery (TA-PI), cerebroplacental ratio (CPR), middle cerebral artery (MCA-PI), umbilical artery (UA-PI).

The comparison of abnormal proportions observed between the arteries in high-risk pregnancy with IUGR from 33 to 35 gestational weeks revealed no statistically significant changes in PI of all arteries. In high-risk pregnancy with IUGR group from 36 to 37 gestational weeks, the most significant pathological changes were found in TA-PI which were also seen in high-risk with IUGR group from 38 to 40 gestational weeks (Table 8). The second detected proportion of pathological changes was in CPR and MCA-PI. The proportion of the least abnormal cases were found in UA-PI.

Table 8. High-risk pregnancy with IUGR group. The comparison of Doppler findings of the umbilical artery (UA-PI), the middle cerebral artery (MCA-PI), cerebroplacental ratio (CPR), and the tibial artery (TA-PI) between 33 and 35, 36 and 37, 38 weeks of gestation and over the last week's examination before delivery. (P - Values ***-p<0.001, **-p<0.01, *-p<0.05).

Comparison between variables (p-values)	**Group**		
	33-35 gestational weeks	36-37 gestational weeks	38-40 gestational weeks
UA-PI vs MCA-PI	0.727	0.619	**0.042**
UA-PI vs CPR	0.323	0.103	**0.002**
UA-PI vs TA-PI	0.246	**0.029**	**<0.001**
CPR vs TA-PI	0.469	0.318	0.268
CPR vs TA-PI	0.192	0.184	**0.024**
CPR vs TA-PI	0.681	0.866	**0.306**

Furthermore, Fig. 18 shows the increasing proportion of abnormal cases in the umbilical artery (UA-PI), middle cerebral artery (MCA-PI), cerebroplacental ratio (CPR) and the tibial artery (TA-PI). A statistically significant acceleration of the tibial artery PI in high-risk pregnancy with IUGR group from 36 to 37 gestational weeks and from 38 to 40 gestational weeks.

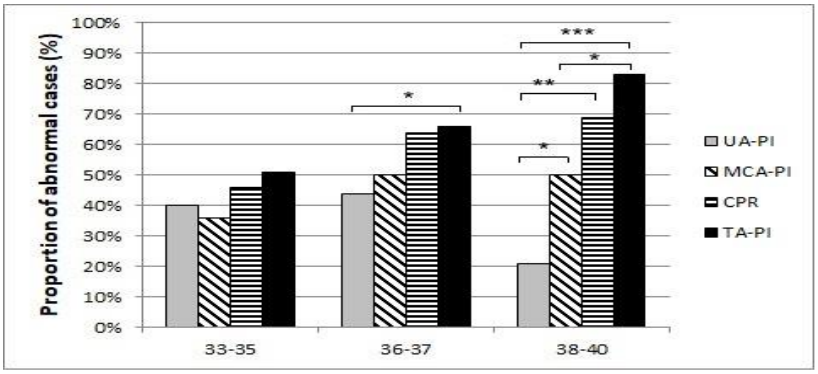


Figure 18. High-risk pregnancy with IUGR group. The proportion of Doppler findings of abnormal cases in the umbilical artery (UA-PI), the middle cerebral artery (MCA-PI), cerebroplacental ratio (CPR), and the tibial artery (TA-PI) between 33 and 35, 36 and 37, 38 weeks of gestation and during the last examination before delivery. (P - Values ***-p<0.001, **-p<0.01, *-p<0.05).

3.5 Comparative analysis of the mode of delivery

The analysis of the mode of delivery between groups of subjects showed statistically significant results when comparing 3 modes of delivery (labor induction, cesarian section, spontaneous labour). Statistically significant results were found in low-risk group in terms of spontaneous delivery, compared to high-risk with IUGR and high-risk without IUGR groups (Table 9).

Table 9. Comparison of groups of participants by mode of delivery. Statistical tests (*Fisher's exact test for count data simulated p-value (based on 2000 replicates, ±Pearson's Chi-squared test)

Characteristics	**Groups**				**P-value**
	All participants n=126 (n,(%))	**High-risk pregnancy without IUGR group n=56 (n,(%))**	**High- risk pregnancy with IUGR group n=53 (n,(%))**	**Low-risk pregnancy group n=17 (n,(%))**	
Labor induction* (LI), n (%)	34 (27)	14 (26.4)	20 (35.7)	0 (0)	p<0.005
Cesarean section* (elective and emergency) (CS), n (%)	32 (25.4)	15 (28.3)	16 (28.6)	1 (5.9)	p=0.131
Elective cesarean section* (ECS), n (%)	16 (12.6)	8 (14.2)	8 (15.0)	0 (0)	p=0.131
Spontaneus labor± (SL), n(%)	60 (47.6)	24 (45.3)	20 (35.7)	16 (94.1)	p<0.001

In high-risk pregnancy with IUGR group, the differences in the mode of delivery were statistically not significant, however, the trend was obvious in the abnormal tibial artery group. The participants of this group compared with the normal tibial artery group underwent more cesarean sections, respectively 29.3% and 25% (Table 10).

Table 10. Comparison of the mode of delivery in high-risk pregnancy with IUGR group with normal and abnormal TA cases. Statistical tests *Fisher's Exact Test for Count Data simulated p-value (based on 2000 replicates, ±Pearson's Chi-squared test.

Characteristics	Groups			P-value
	High-risk pregnancy with IUGR group n=53	Normal TA-PI group (TA>5 and <95 percentile) n=12	Abnormal TA-PI group (TA>95 percentile) n=41	
Labor induction*, n (%)	14 (26.4)	4 (33.3)	10 (24.4)	p=0.711
Cesarean section*, n (%)	15 (28.3)	3 (25.0)	12 (29.3)	p>0.999
Spontaneus labor±, n (%)	24 (45.3)	5 (41.7)	19 (46.3)	p=0.775

Furthermore, opposite trends were observed in the mode of delivery of high-risk pregnancy without IUGR group. The differences were not statistically significant, the trend was observed in the normal tibial artery group. The participants of this group underwent more cesarean sections (30.3%) when compared with those from the abnormal tibial artery group (26.1%) (Table 11).

Table 11. Comparison of the mode of delivery in high-risk pregnancy without IUGR group with normal and abnormal TA cases. Statistical tests (*Pearson's Chi-squared test)

Characteristics	Group			P-value
	High-risk pregnancy with IUGR (n=56)	Normal TA-PI group (TA>5 and <95 percentile) (n=33)	Abnormal TA-PI group (TA>95 percentile) (n=23)	
Labor induction*, n (%)	20 (35.7)	11 (33.3)	9 (39.1)	p=0.656
Cesarean section*, n (%)	16 (28.6)	10 (30.3)	6 (26.1)	p=0.731
Spontaneous labor*, n (%)	20 (35.7)	12 (36.4)	8 (34.8)	p=0.903

Table 12. The Cesarean section was performed due to fetal hypoxia.

Cesarean section performed due to fetal hypoxia (n=4)	Group	
	Normal TA-PI group (TA>5 and <95 percentile)	Abnormal TA-PI group (TA>95 percentile)
High-risk pregnancy with IUGR (n=2)	0	2
High-risk pregnancy without IUGR (n=2)	1	1

Furthermore, we analyzed the cases of cesarian section performed due to fetal hypoxia. Thus, four patients out of all the cesarean sections performed had acute fetal hypoxia indication for cesarean section. In all, 75% of those women had abnormal TA-PI before delivery (Table 12).

3.6 Perinatal outcomes

The comparison of all the three groups of newborns showed a statistically significant difference between the gestational age of newborns. In high-risk pregnancy without IUGR group and high-risk pregnancy with IUGR group, the gestational age was significantly lower compared to the third low-risk pregnancy group (Table 13).

Table 13. Perinatal outcomes. Statistical tests (IQR - interquartile range, df- degree of freedom, M- mean, SD - standard deviation
[a]p value by independent-samples Kruskal-Wallis test (Pairwise Comparisons of Group by Dunn's test) [b]p value by Chi-Square tests
[c]p value by One-Way ANOVA (Pairwise Comparisons of Group by Bonferroni test).

Characteristics	**Groups**				**P-value**
	All participants (n=126)	**High-risk pregnancy without IUGR group (n=56)**	**High-risk pregnancy with IUGR group (n=53)**	**Low-risk pregnancy group (n=17)**	
Gestational age at delivery (week) Median [IQR]	38.5 [37.0-39.0]	39.0 [38.0-39.0] *	38.0 [37.0-39.0]**	40.0 [39.0-40.0] *,**	**p<0.001; *,**p<0.05**
Meconium in amniotic fluid, n (%)	4 (3.2)	2 (3.6)	2 (3.8)	0 (0%)	p=1.0
Meconium aspiration syndrome, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Neonate gender, n (%) Male Female	61 (48.4) 65 (51.6)	28 (50.0) 28(50.0)	22 (41.5) 31 (58.5)	11 (64.7) 6 (35.3)	p=0.238
Birth weight (g), M(SD)	2956.3(684.7)	3304.6(538.4)*,**	2371.7(409.2) *,***	3631.5(284.8) **,***	**p<0.001[b]; *,**,***p<0.05**
Birth weight <5th percentile, n (%)	32 (25.3)	0 (0.0) *	32 (100)*,**	0 (0) **	**p<0.001[a]; *,**p<0.05**
Birth weight <10th percentile, n (%)	53 (42)	0 (0.0) *	53 (100) *,**	0 (0) **	**p<0.001[a]; *,**p<0.05**
Umbilical artery pH, Median [IQR]	7.29 [7.23-7.34]	7.29 [7.2-7.33] *	7.33 [7.29-7.36] *,**	7.28 [7.21-7.32] **	**p=0.026[a]; *,**p<0.05**

Umbilical artery pH <7.35, n (%)	100 (80.0)	44 (80.0)	40 (75.5)	16 (94.1)	p=0.247[b]
Umbilical artery pH <7.2, n (%)	22 (17.6)	14 (25.5)	5 (9.4)	3 (17.6)	p=0.092[b]
Umbilical artery pH <7, n (%)	1 (0.8)	1 (1.8)	0 (0)	0 (0)	p=1.0[b]
Apgar score at 5 min. Median [IQR]	10.0[9.0-10.0]	10.0[9.0-10.0]	9.5[9.0-10.0] *	10.0[10.0-10.0] *	**p=0.028[a]; *p<0.05**
Need for respiratory support after birth, n (%)	11 (8.7)	5 (8.9)	5 (9.4)	1 (5.9)	p=1.0[b]
Neonatal jaundice, n (%)	26 (20.6)	10 (17.9)	15 (28.3)	1 (5.9)	p=0.114[b]
Neonatal hypoglycemia, n (%)	9 (7.3)	2 (3.6)	6 (4.8)	1 (5.9)	p=0.271[b]

Meanwhile, fetal gender, median gestational age, median of newborn weight, fetal weight of <5 percentile and <10 percentile showed no statistical significance. In all, respiratory support was necessary for 12.2% of newborns in the group of pathological tibial artery PI which accounted for 8.4% of the total cases. On the contrary, no respiratory support for newborns was needed in the cases of normal tibialis parameters.

In the group with the tibial artery PI>95 percentile, respiratory support was applied to 5 newborns, while in normal tibialis group, there were 0 newborns. Obviously, even though respiratory support was provided to 5 newborns out of 53 cases with TA PI>95 percentile, there are no statistical methods available to validate the sample of 0 and 5.

Furthermore, the groups with jaundice revealed no significant differences. However, the group with the tibial artery PI>95 percentile comprised 29.3 percent of newborns with jaundice, while the normal group involved 25% cases with jaundice. Similar trends were observed in the group of newborns with hypoglycemia with 5 newborns diagnosed with this disorder in the pathological tibial artery PI group, while there was only one newborn in the normal tibial artery PI group.

Even though these trends did not reveal a statistical significance, they allow an assumption of a statistical significance likely to occur if the sample is enlarged.

The comparison of normal and abnormal PI values of the tibial artery with perinatal outcomes in high-risk pregnancy with IUGR group showed a higher percentage of neonatal jaudince and hypoglycemia in abnormal TA-PI group, however, it was not statistically significant (Table 14).

Table 14. Comparison of perinatal outcomes in normal (TA-PI >5 and <95 percentile) and abnormal (PI>95 percentile) PI values groups when the tibial artery PI was recorded over the last week before delivery in high-risk pregnancy with IUGR group, by using statistical tests* (*Fisher's exact test, ±Wilcoxon rank sum test).

Characteristics	**Groups**			**p-value**
	Overall, N = 53	**TA PI >95 percentile, N = 41**	**TA-PI >5 and <95 percentile), N = 12**	
Fetal weight* percentile <5	33 (62.3%)	24 (58.5%)	9.0 (75%)	0.500
Oligohydramnios*AFI <5	2 (3.8%)	2 (4.9%)	0 (0%)	>0.999

Modified biophysical profile* (abnormal)	2 (3.8%)	2 (4.9%)	0 (0%)	>0.999
Meconium*	2 (3.8%)	1 (2.4%)	1 (8.3%)	0.405
Meconium aspiration syndrome	0	0	0	-
Umbilical artery pH± Median (IQR)	7.33 (7.29, 7.35)	7.33 (7.30, 7.35)	7.31 (7.28, 7.37)	0.725
Respiratory support*	5 (9.4%)	5 (12.2%)	0 (0 %)	0.577
Newborn jaundice*	15 (28.3%)	12 (29.3%)	3 (25%)	>0.999
Newborn hypoglycemia*	6 (11.3%)	5 (12.2%)	1 (8.3%)	>0.999
APGAR score± 1 min Median (IQR)	9.00 (8.00, 9.00)	9.00 (8.00, 9.00)	9.00 (9.00, 9.00)	0.500
APGAR score± 5 min Median (IQR)	9.50 (9.00, 10.00)	9.00 (9.00, 10.00)	10.00 (9.00, 10.00)	0.487
Fetal weight Z score+ Median (IQR)	-1.98 (-2.87, -1.42)	-1.92 (-2.88, -1.39)	-2.12 (-2.29, -1.47)	0.978
Birth lenght± cm Median (IQR)	48.0 (46.0, 50.0)	47.5 (45.8, 50.0)	48.0 (47.8, 50.0)	0.352
UA pH < 7	0 (0%)	0 (0%)	0 (0%)	-
UA pH* < 7.2	5 (9.4%)	5 (12.2%)	0 (0%)	0.577
UA pH* < 7.35	37.0 (69.8%)	29.0 (70.7%)	8.0 (66.7%)	>0.999

The comparison of normal and abnormal PI values of the tibial artery with the perinatal outcomes in high-risk pregnancy without IUGR group showed no statistically significant results (Table 15).

Table 15. Comparison of the perinatal outcomes in normal (TA-PI >5 and <95 percentile) and abnormal (PI>95 percentile) PI values groups when the tibial artery PI was recorded over the last week before delivery in high-risk pregnancy without IUGR group, by using statistical tests (*Fisher's exact test ±Wilcoxon rank sum test)

Characteristics	Groups			p-value
	Overall, N = 56	TA PI >95 percentile, N =33	TA PI >5 and <95 percentile, N = 23	
Week of birth± Median (IQR)	39 (38.00, 39.00)	39 (37.50, 39.00)	39 (38.00, 39.00)	0.731
Newborn weight± g Median (IQR)	3,265 (2,950, 3,624)	3,180 (2,915, 3,395)	3,430 (3,170, 3,640)	0.127
Oligohydramnios*	2 (3.6%)	1 (4.3%)	1 (3.0%)	>0.999
Polyhydramnios*	3 (5.4%)	1 (4.3%)	2 (6.1%)	>0.999
Modified biophysical profile*	2 (3.6%)	1 (4.3%)	1 (3.0%)	>0.999
Meconium*	2 (3.6%)	0 (0%)	2 (6.1%)	0.507
Umbilical cord pH± Median (IQR)	7.30 (7.20, 7.33)	7.31 (7.23, 7.34)	7.27 (7.20, 7.33)	0.293
Respiratory support*	5 (8.9%)	1 (4.3%)	4 (12.1%)	0.639
Newborn jaundice*	10 (17.9%)	5 (21.7%)	5 (15.2%)	0.725
Newborn hypoglycemia*	2 (3.6%)	1 (4.3%)	1 (3.0%)	>0.999
APGAR score± 1 min Median (IQR)	9 (9.00, 9.00)	9 (9.0, 9.0)	9 (9.0, 9.0)	0.490
APGAR score± 2 min Median (IQR)	10 (9.00, 10.00)	10 (9.25, 10.00)	10 (9.00, 10.00)	0.897
Fetal weight Z score± Median (IQR)	0.62 (-0.16, 1.13)	0.61 (-0.32, 0.97)	0.73 (-0.01, 1.15)	0.657
Birth lenght± cm Median (IQR)	52 (49.75, 53.00)	52 (49.50, 53.00)	52 (50.00, 54.00)	0.867
UA pH* < 7	1 (1.8%)	0 (0%)	1 (3.0%)	>0.999
UA pH* < 7.2	12 (21.4%)	5 (21.7%)	7 (21.2%)	>0.999
UA pH* < 7.35	44 (78.6%)	18 (78.3%)	26 (78.8%)	>0.999

DISCUSSION

To our knowledge, this is the first study which has investigated and described the characteristics and longitudinal dynamics of the fetal tibial artery from 33 to 40 weeks of gestation in low-risk and high-risk pregnancies, and the results were compared with perinatal outcomes.

In low-risk pregnancy, our study revealed no benefit of TA-PI Doppler monitoring method, compared to common fetal surveillance techniques. Also, this low-risk pregnancy group showed no abnormal PI changes in the tibial artery in any of the weeks, had no significant adverse perinatal outcomes. On the contrary, the tibial artery parameters in high-risk pregnancy groups with and without IUGR revealed significant changes which afterwards were compared to other fetal arteries and fetal well-being surveillance tests. The findings of this study showed that this method is likely to facilitate monitoring fetuses in clinical practice. Also, this study shows a non-homogenous distribution by mode of delivery, which may have influenced the results of perinatal outcomes. It may be assumed that if the study had been conducted into only one specific type of delivery, more relevant study outcomes could have been obtained. Further research studies may focus on only one category of mode of delivery.

The principal findings of this analysis have shown that TA-PI in high-risk pregnancy with IUGR first rises above the normal range and becomes abnormal, being the first sign of occurring changes in the fetal arteries compared to measurements of other fetal arteries in high-risk pregnancy without IUGR fetuses and low-risk pregnancy. This increase of the TA-PI is associated with a remarkable constriction of the fetal peripheral arteries as a possible adaptation before the centralization of blood flow in the fetus.

Emphasis may be laid on previous literature presenting contrary findings of the research into peripheral arteries, the fetal femoral artery, the interaction of femoral artery changes that were not associated with the evidence of risk for a deteriorating fetal condition, however, the study participants were only women with up to 35 weeks of pregnancy [22], while our data was taken weekly until delivery, the median of 39 gestational weeks. Moreover, in animal studies, increased TA-PI changes were characterized by a progressive increase in progressing fetal hypoxia as a mechanism of cerebral circulation for the development of adaptive changes [85]. Our study findings are essential in terms of the clarification of the pathophysiological pathways and risk factors determining the deteriorating fetal condition before delivery and in elucidating the role of the tibial artery Doppler examination as an additional tool to the

existing fetal surveillance techniques deployed in monitoring fetuses in high-risk pregnancy.

Our findings suggest that the peripheral artery Doppler examination better reflects monitoring of fetal well-being in high-risk pregnancy with late-onset IUGR. Antenatal screening and monitoring with fetal surveillance tests in the third trimester are likely to have a major impact on adverse perinatal outcomes. The time of delivery of fetuses in high-risk pregnancy has always been a clinical concern. Previous studies have investigated surveillance techniques applied in high-risk pregnancy with different parameters chosen to evaluate intrauterine fetal condition, therefore, most researchers agree with a similar fetal surveillance management to be used in clinical practice. Our study has included the NST/CTG as the most used fetal surveillance techniques which benefit from fetal heart rate and movements. Meanwhile, our research findings agree with current evidence provided by previous studies [110] on fetal surveillance that NST and CTG can rarely or at times show false negative results. Therefore, adding ultrasound scanning to fetal surveillance testing tools may result in a much better available technique to date which not only allows to detect the deteriorating fetal condition more accurately, but also integrates the biophysical and modified biophysical profiles into the daily fetal surveillance practice. Moreover, these two techniques are more reliable than NST or UG alone. Furthermore, our data agrees with the data provided by current research studies [111] that despite the normal NST/CTG, the biophysical profiles/modified BP can be abnormal, what is supported by our findings, too. Also, our study has revealed that the modified BP was abnormal due to the confirmed oligohydramnios while NST was within the normal range. The greatest benefits of ultrasound are its availability with the Doppler technique allowing for fetal surveillance to become one of the most effective techniques used for evaluating fetal surveillance parameters in ultrasound monitoring. Additionally, Doppler has its own indications in each of high-risk pregnancy conditions, however, in uncomplicated pregnancies, it has no additional value.

Moreover, this study reveals several aspects that are crucial for improving the prognostic value of fetal surveillance techniques. Our model consisted of currently familiar fetal surveillance techniques (NST, CTG, biophysical profile, modified biophysical profile, ultrasound, and ultrasound Doppler). All these techniques were used according to the established obstetrical guidelines and the current consensus [96]. Additionally, we included the parameters of the peripheral artery - the tibial artery Doppler technique for fetal surveillance. Our study has revealed that the third trimester Doppler ultrasound performed on fetuses from 33rd gestational week to birth has the benefit of detecting a

possible deteriorating fetal condition, especially in IUGR fetuses. It is noteworthy that adding the peripheral artery Doppler ultrasound examination to the surveillance techniques may result in the improvement of perinatal outcomes.

Our study has revealed that UA did not indicate significant changes in near term subjects in any of the followed groups. Our findings correspond to the results obtained by previous studies reporting that the parameters of UA reflect the placental blood flow, however, they do not reflect the fetal condition in late-onset IUGR [101]. Therefore, while estimating perinatal risks, it is important to perform the measurements of other fetal blood vessels. The data suggests that the resistance of the middle cerebral artery decreases due to fetal hypoxemia even if the resistance of UA shows normal rates what was also revealed by our findings [112-114]. Furthermore, our study has indicated that MCA-PI and CPR showed a progressive decrease from inclusion to delivery in high-risk pregnancy with IUGR group but was not found in high-risk pregnancy without IUGR fetuses.

The findings of our study indicate that MCA-PI showed fewer abnormal values than those obtained after combining MCA-PI with CPR, especially in high-risk pregnancy with IUGR fetuses. Importantly, Z-scores of CPR and MCA were close to pathological values, however, more significant changes were found in CPR than in MCA alone, especially in high-risk pregnancy with IUGR group. The most significant changes were found in TA-PI progressing with the increasing gestational age, again mostly in high-risk pregnancy with IUGR group, but not in high-risk pregnancy without IUGR group. As reported by recent ISUOG guidelines, CPR [115] is the most recommended parameter to monitor in late-onset IUGR fetuses. Our study has found that the use of isolated UA Doppler is likely to show a lower or no evaluation of the fetal condition, while a more advanced measurement is CPR (MCA/UA=CPR), whereas TA-PI Doppler measurement suggests that the changes in the peripheral arteries are detected earlier. Moreover, the changes in TA-PI were more demonstrative only when the fetal weight was <10 percentile or less <5th percentile which allows the confirmation of the fact that the normal fetal development in the uterus depends on the placental function.

Taking into account that TA is a tiny fetal vessel, researchers need to be equipped with the necessary practical skills and qualifications to ensure the accuracy of the Doppler parameter values. Moreover, in our research study, all the measurements on the participants were conducted by a single researcher who met the researcher's requirements. Also, it is worth mentioning that under unfavorable pandemic conditions, this study has included a significant sample

of participants with targeted high-risk pregnancy pathologies. In all, we succeeded in obtaining statistically significant results from the data collected, however, in some cases the sample could have been larger to demonstrate more relevant findings.

Our data suggests a possible value of monitoring the peripheral arteries to be deployed as an additional surveillance tool in assessing pregnancies in the third trimester. It could possibly have a significant collaboration together with other techniques that are used in perinatological clinical practice, especially in monitoring high-risk pregnancy. Along the same line, previous studies show the elevation of the tibial artery PI in high-risk pregnancy with IUGR fetuses from 36 weeks of gestation [21]. Moreover, as revealed by the study of 23-42 GA fetuses, monitoring of TA-PI allows detecting early alterations in the fetal blood circulation [28].

This dissertation shows that the selection of TA- PI Dopplerometry method in high-risk pregnancy can supplement current surveillance methods if applied for monitoring high-risk pregnancy with late IUGR. The application of this additional tool can improve perinatal outcomes by more accurately evaluating fetal well-being and assisting in clinical decision-making regarding the timing of delivery.

In general, the results of this dissertation suggest that the choice of the fetal surveillance technique of the tibial artery in low-risk pregnancy can hardly supplement other familiar techniques. Significantly, it can bring benefits if used for evaluating fetal well-being and considering the timing of delivery in surveilling close to term high-risk pregnancy without IUGR and mostly high-risk pregnancy with late-onset IUGR.

The uniqueness of our study is that we focused on the peripheral arteries while in most cases, fetal surveillance methods are used to investigate the central, but not peripheral arteries. This method can more accurately reflect the onset of a deteriorating fetal status, compared to other surveillance techniques. The most benefit of this technique was observed in high-risk pregnancy with late IUGR.

STRENGTHS AND FUTURE PERSPECTIVES

The main strength of the study is its uniqueness in terms of its methodology and focus on the peripheral fetal circulation. The measurements were conducted by a single researcher using the same equipment. Furthermore, unlike other studies, we analyzed both pathological and normal values allowing a better interpretation of the results obtained from the subjects of different gestational age and different maternal, fetal, or newborn backgrounds.

Both this study and the methodology applied for the examination of the tibial artery are unique and rare in the research world because of a specific technique used to obtain the accurate values of appropriate measurements of the fetal tibial artery.

There are several potential perspectives for our study. First, emphasis must be laid on the competitive advantage and the clinical utility of the peripheral artery Dopplerometry which could be included in fetal surveillance for high-risk pregnancy with IUGR and without IUGR. Second, it could serve as an additional tool for obstetricians-gynecologists in decision making since the algorithms of the right surveillance frequency and techniques methods for high-risk pregnancy with late-onset IUGR have not been completely validated yet. This method should be included in multicenter trials to validate this antenatal surveillance test for fetal well-being assessment and to consider adding this tool to the global recommendations.

To the best of our knowledge, this is the first longitudinal study conducted on high-risk pregnancy fetuses with a mean follow-up period of five weeks aiming to identify, compare and analyze the changing patterns of Doppler parameters of the central and peripheral arteries. This study also focuses on delineating the clinical features and the best timing for high-risk pregnancy with IUGR fetuses.

LIMITATIONS

It is essential to highlight that the present study has several limitations. There was some covariate data missing in some of the subjects, which prevented us from including the entire sample of the enrolled participants to conduct the present analysis. In addition, our study was conducted under the global COVID-19 pandemic with the restrictions posed by the government in health institutions for physicians with limited time allocated for both contacts with patients and face-to-face examination. Therefore, our study focused on a small sample size of subjects with no cases of stillbirth or newborns with severe asphyxia. Further research including more adverse outcomes can benefit in more statistically significant results.

CONCLUSIONS

1. Measurements of the peripheral fetal tibial artery Doppler pulsatility index in low-risk pregnancy have no additional predictive value for fetal perinatal outcomes. The values of Doppler ultrasound pulsatility index of the fetal tibial artery, middle cerebral artery, umbilical artery and the cerebroplacental ratio were normal in low-risk pregnancies.

2. Measurements of the peripheral fetal tibial artery Doppler pulsatility index in high-risk pregnancy (hypertensive disorders, cholestasis of pregnancy, diabetes, COVID-19 infection) without intrauterine growth restriction may have an additional value for fetal perinatal outcomes in full term pregnancy. The fetal tibial artery deviated most significantly from the norm from 39-40th gestational week and a significant abnormal increase was observed, meanwhile, Z values of the middle cerebral artery, umbilical artery and the cerebroplacental ratio, remained within normal ranges.

3. Measurements of the peripheral fetal tibial artery Doppler pulsatility index in high-risk pregnancy (hypertensive disorders, cholestasis of pregnancy, diabetes, COVID-19 infection) with intrauterine growth restriction have an additional value for perinatal outcomes from 35th gestational week. The parameters of the fetal tibial artery deviated most significantly from the normal at 35th gestational week and showed a significant abnormal rise among all measured arteries.

PRACTICAL RECOMMENDATIONS

1. The tibial artery pulsatility index Dopplerometry is not recommended for monitoring fetal well-being in low-risk pregnancy, also non-qualified specialists may find it not easy to use.
2. The tibial artery Dopplerometry is recommended as an additional technique for fetal surveillance while on the follow up of high-risk pregnancy (hypertensive disorders, cholestasis of pregnancy, diabetes, COVID-19 infection) with late-onset intrauterine growth restriction from 35th week of pregnancy for the detection and monitoring of a deteriorating fetal condition, in search for the tibial artery pulsatility index increase of more than >95 percentile.

SANTRAUKA LIETUVIŲ KALBA

SANTRUMPOS

BA	Blauzdos arterija
CPO	Cezario pjūvio operacija
CPS	Cerebroplacentinis santykis
VAS	Vaisiaus augimo sulėtėjimas
NVS	Numatomas vaisiaus svoris
PI	Pulsacijos indeksas
RI	Rezistentiškumo indeksas
VA	Virkštelės arterija
VL	Veninis latakas
VPA	Vaisiaus pilvo apimtis

ĮVADAS

Didelės rizikos nėštumas nustatomas 6–33 proc. nėščiųjų [1-2]. Moteris, kurioms nustatytas didelės rizikos nėštumas, reikia papildomai ištirti, ištyrus taikyti specifinį gydymą ir atitinkamą antenatalinę priežiūrą. Didelės rizikos nėštumas apibrėžiamas kaip įvairios nėščiosios ir vaisiaus patologinės būklės bei ligos, didinančios perinatalinę riziką [1]. Motinos, vaisiaus ar placentos patologinė būklė gali lemti intrauterininę žūtį [2]. Atliktame tyrime įtraukėme nėščiąsias, kurioms buvo diagnozuota patologija, kuri galėjo būti susijusi su kraujagyslių pažaida ir galimai lemti vaisiaus blogėjančią intrauterininę būklę ir/ar vaisiaus augimo sulėtėjimą. Terminu VAS apibūdinama būklė, kai numatomas vaisiaus svoris atitinkamą nėštumo savaitę yra mažesnis nei 10 procentilis. Atsižvelgiant į nėštumo savaitę diagnozės nustatymo metu, VAS skirstomas į ankstyvąjį (< 32 savaitės) ir vėlyvąjį (≥ 32 savaitės).

Tinkamu laiku nustatytas didelės rizikos nėštumas – ypač VAS, ir tinkamas motinos bei vaisiaus būklių stebėjimas lemia palankesnes perinatalines baigtis [9]. Akivaizdu, kad tradiciniai vaisiaus augimo stebėjimo metodai, pavyzdžiui, vėlyvojo nėštumo metu atliekamas gimdos dugno aukščio matavimas, yra nepakankami. Norint geriau išaiškinti ir nustatyti vėlyvąjį VAS, reikia atlikti papildomą tyrimą, pavyzdžiui, 3-iojo trečdalio ultragarsinį tyrimą. Siekiant įvertinti vaisiaus būklę, galimi įvairūs vaisiaus stebėjimo tyrimai gimdos dugno aukščio matavimas, NST / KTG, biofizinis profilis arba modifikuotas biofizinis profilis, vaisiaus biometrija ir VA, VSA, GK bei VL dopleriniai matavimai [11–15].

Pasauliniu mastu atliekami tyrimai parodė, kad dažniausiai naudojamas VA doplerometrija yra tinkama priemonė blogėjančiai vaisiaus būklei ankstyvojo VAS metu nustatyti [17, 18]. Tačiau šis metodas netikslus vėlyvojo VAS atveju. Fiziologiškai virkštelės arterijos rezistentiškumo indeksas didėjant nėštumo savaitėms palaipsniui mažėja [19]. Yra žinoma, kad vėlyvuoju nėštumo laikotarpiu VA parametrai atspindi tik placentos kraujotaką, tačiau jie nerodo vaisiaus būklės. Svarbu pabrėžti, kad padidėjęs virkštelės arterijos rezistentiškumo indeksas arba pulsacijos indeksas (PI) yra placentos nepakankamumo, bet ne vaisiaus būklės rodiklis [19]. Moksliniai tyrimai rodo, kad norint geriau įvertinti vėlyvojo VAS vaisiaus būklę, būtina atlikti vidurinės smegenų arterijos doplerometrija (VSA) ir / arba CPS. Tyrimai parodė, kad šie du rodikliai geriau atspindi blogėjančią vaisiaus būklę (20).

Atliekant tyrimus su gyvūnais [21, 28], buvo analizuojami ir vertinami vaisių periferinių arterijų rodikliai sukėlus hipoksijos sąlygas, kai buvo diagnozuotas VAS. Tokiomis aplinkybėmis buvo pastebėti adaptaciniai

kraujagyslių mechanizmai vėlyvojo avių vaisiaus augimo sulėtėjimo atveju. Pristatytas metodas atveria naujas vaisiaus stebėjimo perspektyvas: pateikiami tiksliau išanalizuoti įvairių kraujagyslių doplerio matavimai, kai įtariama blogėjanti vaisiaus būklė.

Mūsų tyrimu siekiama išsamiai apibūdinti ultragarsinio tyrimo reikšmę vertinant doplerometrijos naudą tiriant centrines bei periferines arterijas, kai nustatytas didelės rizikos nėštumas diagnozavus ar nediagnozavus vėlyvąjį VAS, nustatyti ir palyginti neigiamas perinatalines baigtis, kai diagnozuotas padidėjęs periferinės vaisiaus BA-PI.

Tikėtina, kad šis perspektyvusis stebėjimo ir standartizuotas tyrimas pateiks tvirtų ir patikimų įrodymų vėlyvojo VAS stebėjimui taikant centrinių ir periferinių arterijų doplerometrijos metodą, kai atsiranda vaisiaus hipoksijos požymių arba yra placentos nepakankamumas.

Darbo tikslas. Įvertinti vaisiaus blauzdos arterijos doplerometrijos PI prognostinę reikšmę perinatalinėms baigtims didelės rizikos nėštumo metu diagnozavus vaisiaus augimo sulėtėjimą ir jo nediagnozavus.

Darbo uždaviniai. Siekiant įgyvendinti užsibrėžtą tikslą, keliami tokie uždaviniai:

1. Išmatuoti ir palyginti mažos rizikos nėščiųjų vaisiaus blauzdos arterijos, vidurinės smegenų arterijos, virkštelės arterijos doplerometrijos pulsacijos indeksų ir cerebroplacentinį santykį.
2. Išmatuoti ir palyginti vaisiaus blauzdos arterijos, vidurinės smegenų arterijos, virkštelės arterijos doplerometrijos pulsacijos indeksų ir cerebroplacentinį santykį didelės rizikos nėštumo metu (hipertenzinės būklės, diabetas, intrahepatinė nėščiųjų cholestazė, COVID-19 infekcija) nenustačius vaisiaus augimo sulėtėjimo.
3. Išmatuoti ir palyginti vaisiaus blauzdos arterijos, vidurinės smegenų arterijos, virkštelės arterijos doplerometrijos pulsacijos indeksų ir cerebroplacentinį santykį didelės rizikos nėštumo metu (hipertenzinės būklės, diabetas, intrahepatinė nėščiųjų cholestazė, COVID-19 infekcija) nustačius vaisiaus augimo sulėtėjimą.

Darbo aktualumas, naujumas ir mokslinė reikšmė.

Didelės rizikos nėščiųjų, kai nustatytas arba nenustatytas VAS, periferinė vaisiaus kraujotaka iki šiol nei pasaulyje, nei Lietuvoje nebuvo nuodugniai įvertinta analizuojant perinatalines baigtis. Klinikinėje praktikoje trūksta patikimų standartizuotų metodikų stebint vėlyvąjį VAS. Šis perspektyvusis stebėjimo tyrimas pristato mažos ir didelės rizikos nėščiųjų vaisiaus blauzdos

arterijos doplerometrijos kitimus, kurie buvo palyginti su kitais centrinių kraujagyslių doplerometrijos rodikliais, kurie buvo atrinkti pagal naujausias vaisiaus būklės vertinimo gaires. Buvo vertinanami perinataliniai rezultatai mažos ir didelės rizikos nėštumo metu [22, 23, 29, 30-38]. Šis tyrimas unikalus dar ir tuo, kad ultragarsinius matavimus ir kokybinį vertinimą atliko vienas tyrėjas, todėl vertinimo paklaida labai maža.

Siekiant sumažinti su nėštumu susijusių komplikacijų skaičių ir blogas perinatalines baigtis, remiantis anamneze, klinikiniais duomenimis ir ultragarsinio tyrimo rezultatais, individualiai nustatomas nėštumo užbaigimo laikas [29, 39–43]. Iki šiol nėra pakankamai mokslinių tyrimų duomenų apie vaisiaus periferinės kraujotakos doplerinius parametrus (vaisiaus žasto, šlaunies, blauzdos, pėdos arterijų [21, 44–53]).

Įtariant vaisiaus hipoksiją, gydytojams svarbu nustatyti optimalų nėštumo užbaigimo laiką, todėl periferinių kraujagyslių doplerio matavimo tyrimas galėtų būti dar viena papildoma vaisiaus būklės vertinimo ir blogėjančios vaisiaus būklės diagnostikos priemonė, papildanti dabartines perinatologijos praktikoje taikomas metodikas [53–56].

Ginamieji teiginiai

1. Mažos rizikos nėščiosioms vaisiaus blauzdos arterijos pulsacijos indeksų matavimas neturi prognostinės vertės.
2. Didelės rizikos nėščiosioms, kai nediagnozuojamas vaisiaus augimo sulėtėjimas, vaisiaus blauzdos arterijos pulsacijos indeksų matavimas gali turėti papildomos prognostinės vertės, numatant nepalankias perinatalines baigtis artėjant gimdymo terminui.
3. Didelės rizikos nėščiosioms, kai diagnozuojamas vaisiaus augimo sulėtėjimas vaisiaus blauzdos arterijos pulsacijos indeksų matavimas turi reikšmingą papildomą prognostinę vertę.

TYRIMO METODIKA

Tyrimo planas ir dalyviai

Perspektyvusis stebėjimo tyrimas buvo atliktas 2019 m. gegužės–2022 m. gegužės mėn. Vilniaus universiteto ligoninės Santaros klinikų Akušerijos ir ginekologijos centre. Iš viso tyrime dalyvavo 158 nėščiosios (žr. 1 pav.), pasirašiusios informuoto asmens sutikimą dalyvauti tyrime, kurį patvirtino Vilniaus regiono biomedicininių tyrimų etikos komisija (2019 m. gegužės 27 dienos sprendimai: Nr. 2019-05-27, Nr. 2019/5-1137-624, Vilnius, Lietuva).

VULSK per metus registruojama daugiau kaip 3 000 gimdymų, vidutiniškai 800 nėščiųjų per metus hospitalizuojamos į Nėštumo patologijos skyrių. Akušerijos dienos stacionaro skyrius kasmet teikia medicinines paslaugas maždaug 400 nėščiųjų. Kiekvienais metais teikiamos nėštumo patologijos priežiūros ir gydymo paslaugos nustačius tokias diagnozes: tariamasis gimdymas (26 proc.), diabetas (10 proc.), hipertenzinės būklės (9 proc.), nėščiųjų cholestazė (6 proc.), nėščiųjų pykinimas ir vėmimas (7 proc.), Covid-19 infekcija (1 proc.), vaisiaus augimo sulėtėjimas (4 proc.) ir kt.

Tiriamosios buvo suskirstytos į tris pogrupius: mažos rizikos nėščiosios, didelės rizikos nėščiosios su diagnozuotu VAS ir didelės rizikos nėščiosios, kurioms nediagnozuotas VAS.

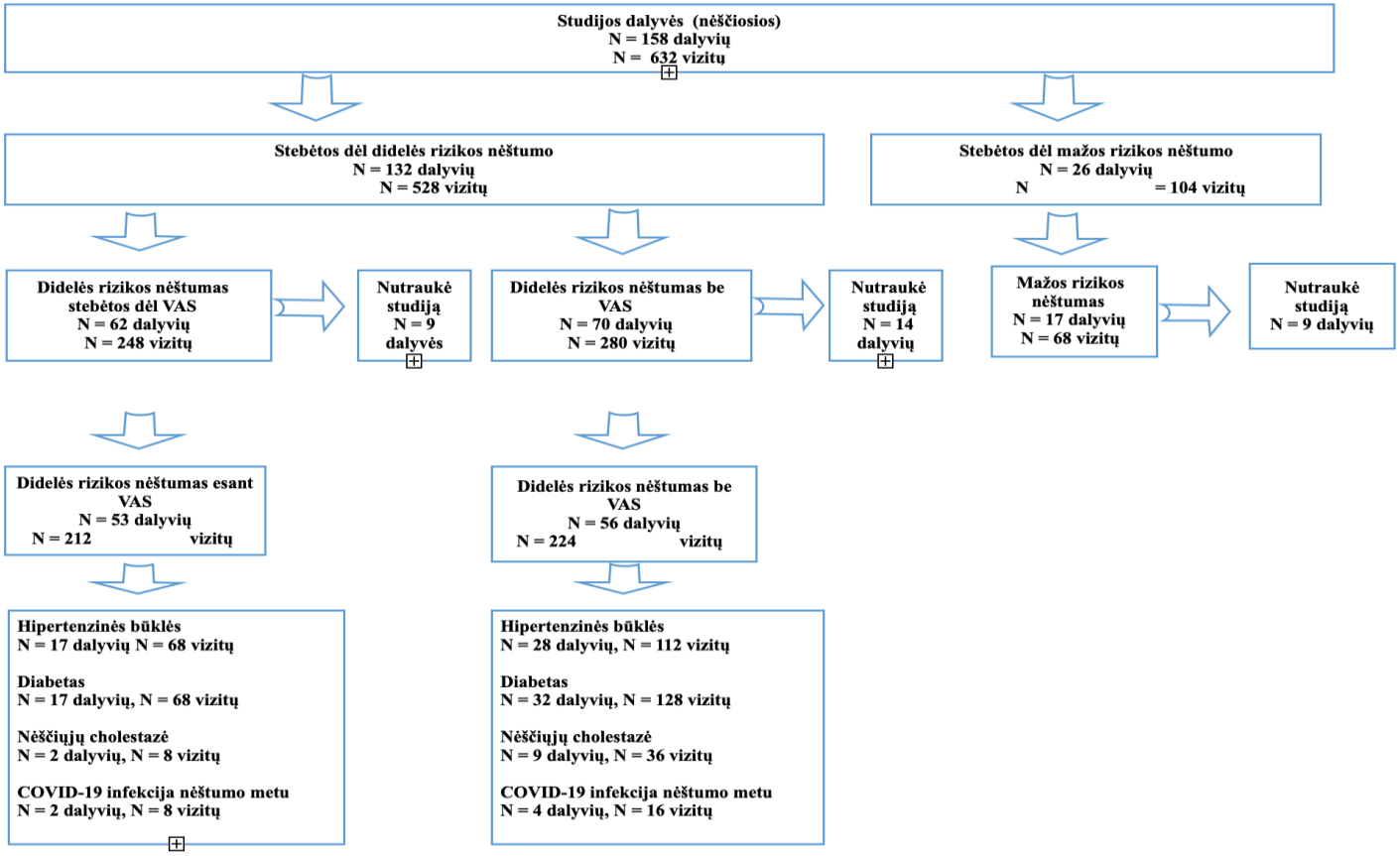
Mažos rizikos nėščiųjų grupę sudarė moterys be nustatytos patologijos. Jos sutiko dalyvauti tyrime ir laikėsi vienodo tyrimo dalyvių stebėjimo protokolo bei tokio pat tyrimo plano kaip ir didelės rizikos grupių nėščiosios.

Didelės rizikos (su VAS ir be VAS) nėščiosios buvo įtrauktos į tyrimą pagal šiuos įtraukties kriterijus:

- Vienvaisis nėštumas.
- Nėštumo trukmė nuo 3 + 0 iki 40 + 0 savaičių.
- Motinos amžius >18–40 metų.
- Didelės rizikos nėštumas:
  - Hipertenzinės būklės.
  - Cukrinis diabetas.
  - Nėščiųjų cholestazė.
  - Koronaviruso liga (COVID-19).
  - VAS (kai numatomas vaisiaus svoris <10% procentilės).

Atmetimo kriterijai:

- Daugiavaisis nėštumas.
- Mažo svorio vaisius atsižvelgiant į nėštumo trukmę.
- Genetinės ar chromosomų anomalijos.
- Vaisiaus apsigimimai.
- Pasitraukimas iš tyrimo dėl asmeninių priežasčių.
- Nėštumas ne mažiau nei 33 + 0 sav.
- Kitos motinos gretutinės ligos.



1 paveikslas. Tiriamųjų kohortos schema.

Tyrimo dalyvės (n = 158) buvo suskirstytos į didelės rizikos nėščiųjų (n = 132) ir mažos rizikos nėščiųjų (n = 26) grupes. Į Akušerijos dienos stacionarą įtrauktų nėščiųjų ir jų vaisiaus būklės stebėjimas vykdavo pirmadieniais. Kiekvienos nėščiosios vaisiaus būklės vertinimas vyko po 4 kartus (n = 632 vizitai). Didelės rizikos nėščiosios buvo suskirstytos į tiriamųjų grupes: didelės rizikos nėštumas su nustatytu VAS (n = 62) ir didelės rizikos nėštumas be atsiradusių VAS (n = 70). Pastarosios buvo suskirstytos į pogrupius pagal gretutinę būklę: hipertenzinės būklės, diabetas, COVID-19 infekcija, intrahepatinė nėščiųjų cholestazė. Tyrime nusprendė nebedalyvauti 32 dalyvės: 9 iš didelės rizikos nėščiųjų grupės su nustatytu VAS, 14 iš didelės rizikos nėščiųjų grupės be VAS, 9 iš mažos rizikos nėščiųjų grupės. Nutraukimo priežastys buvo šios: neatitiko tyrimo kriterijų dėl atsiradusių nėštumo komplikacijų, diagnozuotas mažo svorio vaisius, pandemijos apribojimai ligoninėje; pasitraukė savo noru (žr. 1 pav.).

Per pirmąjį vizitą surinkti šie motinos anamnezės duomenys:

1. Amžius.
2. Tautybė.
3. Nėštumo trukmė remiantis paskutinių mėnesinių data ir / arba pirmojo trečdalio ultragarso duomenis.
4. Nėštumai praeityje.
5. Gretutinės ligos.
6. Dabartinė nėščiosios sveikatos būklė.
7. Dabartinė vaisiaus sveikatos būklė.

Vaisiaus būklės vertinimui pasitelkti tyrimai:

1. Nestresinis testas (NST).
2. Ultragarsinis tyrimas.
3. Modifikuotas biofizinis profilis.

Vaisiaus būklės vertinimo metodika:

1. Savaitinis NST buvo atliekamas tokia tvarka: davikliai juostomis buvo pritvirtinami prie nėščiosios pilvo sienos siekiant nustatyti vaisiaus širdies ritmo dažnį ir motinos suvokiamus vaisiaus judesius. Tyrimo trukmė 20–30 minučių, kol buvo užregistruojamos dvi ar daugiau akceleracijos (15 k./min. ar daugiau virš bazinės linijos), trukusios 15 sekundžių ar ilgiau.
2. Modifikuotas biofizinis profilis (modifikuotas BFP) kiekvienai tyrimo dalyvei buvo atliktas NST, derinant jį su vaisiaus vandenų kiekio vertinimu ultragarsu.

3. Ultragarsinį vertinimą atliko vienas tyrėjas. Matavimai buvo atlikti pasitelkus ultragarsinę sistemą *GE Health Care Voluson S8*, C1-5 daviklį ir spalvotą doplerį, padėjusius vizualizuoti kraujagysles ir kraujotaką.
   a. Biometrijos matavimai buvo atliekami kas dvi savaites.
   b. Doplerio matavimai buvo atliekami kas savaitę.

Skenuojant ultragarsu buvo matuojami kiekybiniai ir kokybiniai rodikliai:
1. Automatiniai biometrijos skaičiavimai buvo atlikti pagal Hadlocko lygtį. Jei vaisiaus pilvo apimtis ar numatomas svoris mažiau nei 10 procentilis pagal atitinkamą nėštumo savaitę, diagnozuotas vaisiaus augimo sulėtėjimas.
2. Vaisiaus vandenų indeksas (VVI).
3. VSA doplerinės bangos PI.
4. VA doplerinės bangos PI.
5. BA doplerinės bangos PI.
6. CPS apskaičiavimas: VSA-PI dalijant iš VA-PI.

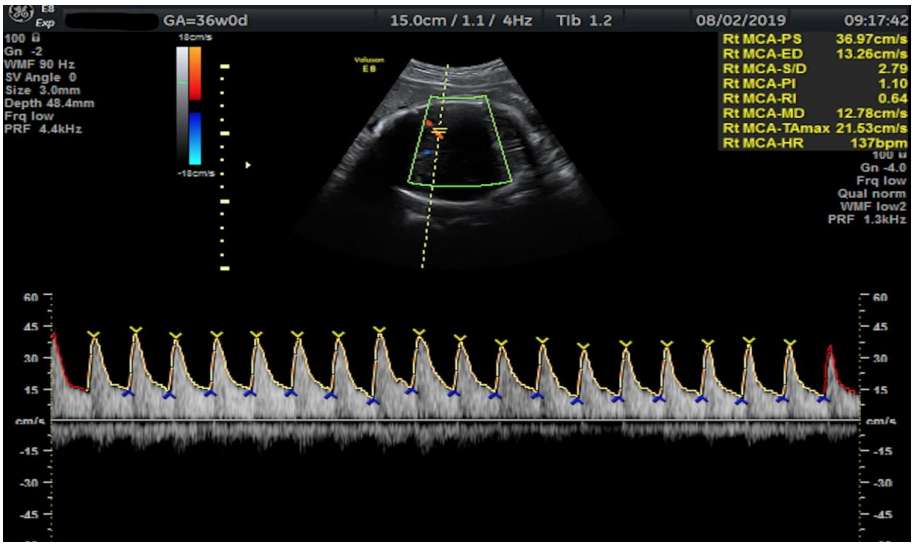
Didelės rizikos nėščiosios su diagnozuotu ir nediagnozuotu VAS buvo suskirstytos į du normalių - BA-PI >5 ir <95 procentilio ir nenormalių - BA-PI >95 procentilio pogrupius.

Doplerometrijos tyrimai iš analizuojamų arterijų buvo atliekami taip: kad būtų užfiksuoti VA-PI iš laisvos virkštelės kilpos, daviklio kampas sufokusuotas žemiau nei 30 laipsnių (žr. 2 pav.). Vaisiaus VSA dopleriniai signalai buvo atliekami išgavus skersinį vaisiaus kaukolės vaizdą, vertinti esantys arčiausiai daviklio. Doplerio fokusas sutelktas proksimaliniame VSA trečdalyje, netoli kraujagyslės Willio rato. Daviklio kampas buvo kuo artimesnis 0 laipsnių.

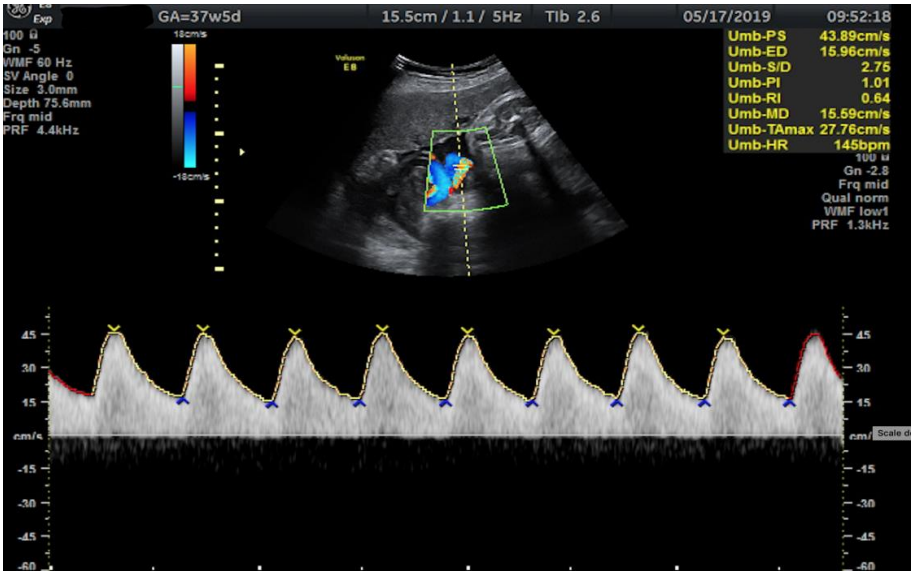
Pagrindinis tyrimo tikslas buvo tiksliai išmatuoti periferinę BA-PI doplerometriją (žr. 3 pav.). Tyrimo metodika buvo sudaryta iš tokių dalių: pirmiausia taikytas doplerio metodas tiriant vaisiaus blauzdą toje vietoje, kur buvo aiškiai matomi blauzdikaulio ir šeivikaulio kaulai. Antra, kampas tarp daviklio ir kaulų buvo sureguliuotas iki 45 laipsnių ar mažiau. Vėliau, siekiant nustatyti priekinę BA, spalvoto doplerio vartai buvo uždėti virš blauzdos kraujagyslės tarp dviejų kaulų (žr. 4 pav.). Kad matavimai būtų tikslesni, doplerio bangos formos indeksai išmatuoti rankiniu būdu, nes aparate *Voluson E8* automatinis BA-PI doplerometrijos skaičiavimas neįdiegtas (žr. 5, 6 pav.).

Reikėtų pabrėžti, kad pagrindinis dėmesys tyrime skiriamas išmatuotų arterijų PI parametrams. PI apibrėžia skirtumą tarp didžiausio sistolinio srauto ir mažiausio diastolinio srauto greičio, padalyto iš per visą ciklą užregistruoto vidutinio greičio. Atliekant tyrimą pavyko išmatuoti visų vaisių BA-PI,

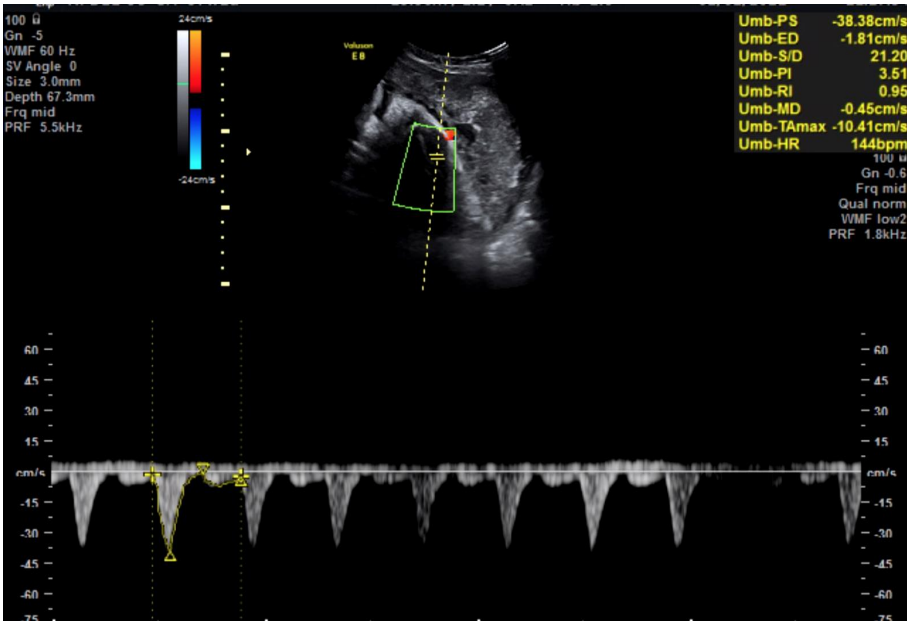
signalai buvo registruojami mažiausiai 5–6 ciklais su vienoda forma ir kraujo tėkmės bangų formų amplitude. Priekinės BA PI buvo lyginamas su BA-PI standartais, paskelbtais *Wisser* ir kt. (21, BA PI procentilės standartai pateikti 1 priede).



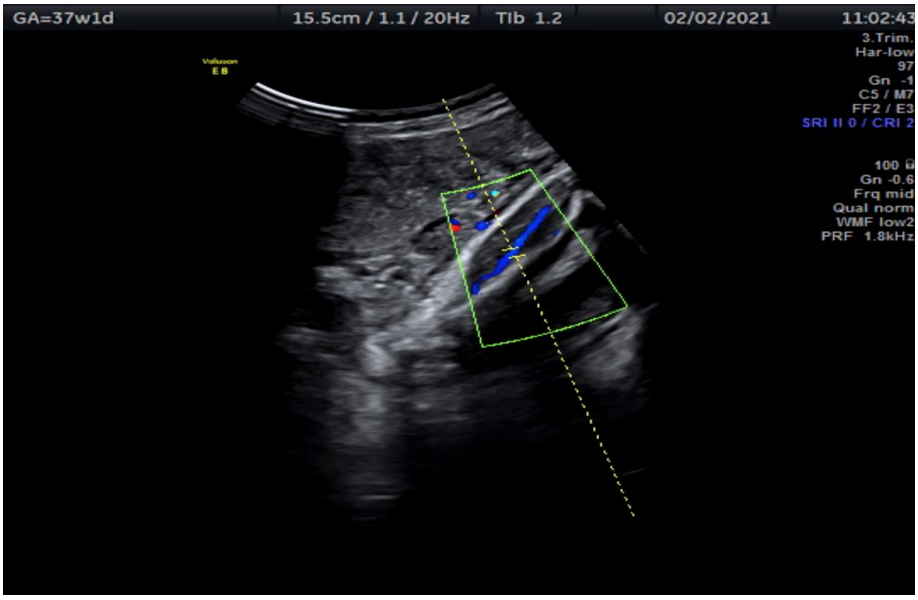
2 paveikslas. Doplerometrinis automatinis VA kraujotakos matavimas (atliktas 37 sav. + 5 d.).



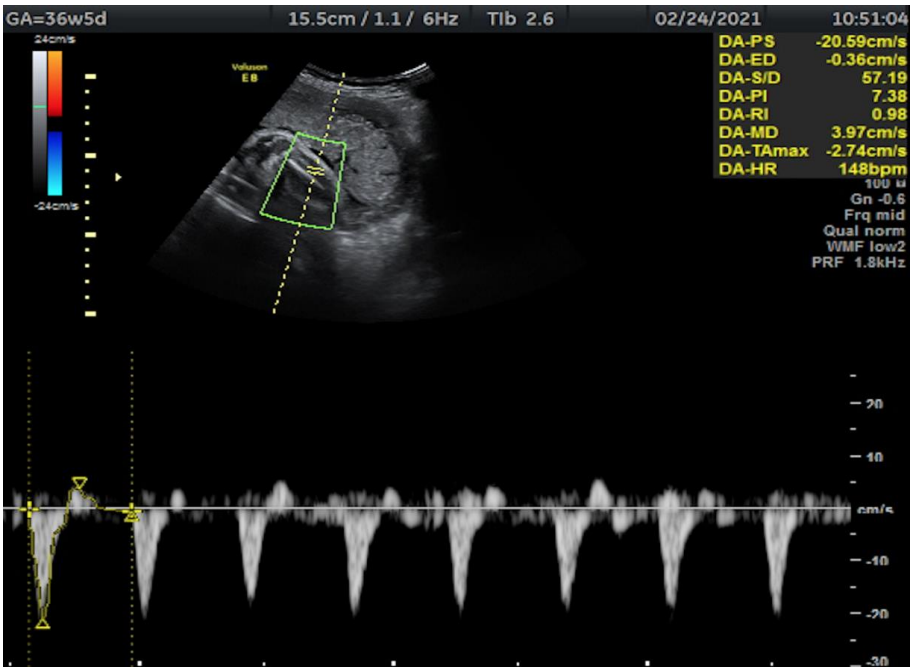
3 paveikslas. Doplerometrinis automatinis VSA kraujotakos matavimas (atliktas 36 sav. + 0 d.)



4 paveikslas. Doplerometrinis vaisiaus BA kraujotakos vizualizavimas tarp blauzdikaulio ir šeivikaulio (atliktas 37 sav. + 1 d.).



5 paveikslas. Doplerometrinis rankinis vaisiaus BA matavimas (atliktas 36 sav. + 5 d.) rodo normalų BA-PI.



6 paveikslas. Doplerometrinis rankinis vaisiaus BA matavimas 36 sav. + 5 d. rodo reversinę BA-PI kraujotaką (PI > 95 procentilio).

Motinos ir naujagimio klinikiniai duomenys surinkti iš Vilniaus universiteto ligoninės Santaros klinikų vidinės duomenų bazės:

- Gimdymo būdas: spontaniškas gimdymas per makštį, gimdymas instrumentiniu būdu arba cezario pjūvis.
- Vaisiaus vandenų spalva.
- Nėštumo trukmė.
- Vaisiaus lytis.
- Gimimo svoris.
- Naujagimio būklės vertinimas pagal Apgar skalę po 5 minučių.
- Laboratoriniai duomenys: virkštelės arterijos pH vertės.
- Naujagimio baigtys:
- Poreikis kvėpuojamajai terapijai.
- Naujagimių gelta.
- Naujagimių hipoglikemija.

Surinkti duomenys buvo saugomi duomenų bazėje. Statistinė jų analizė atlikta taikant programų paketą SPSS 27.0 (angl. *Statistical Package for the Social Sciences*). Analizuojant kiekybinius duomenis, buvo įvertintos pagrindinės jų pasiskirstymo charakteristikos: vidurkis (V), standartinis nuokrypis (SD), mediana [25–75 %], IQR – tarpkvartilis diapazonas.

Atvejų skaičius (n) ir reitingavimo kintamųjų pasiskirstymas pateikiamas procentais. Hipotezėms dėl skirstinio normalumo patikrinti buvo naudojamas Kolmogorovo-Smirnovo testas. Normaliojo skirstinio kiekybinės reikšmės buvo lyginamos naudojant parametrinius kriterijus, o eilės kintamieji ir nenormaliai pasiskirsčiusios kiekybinės reikšmės buvo įvertintos neparametriniais testais. Pasirinktas 95 proc. pasitikėjimo lygis ir reikšmingumo lygis p = 0,05. Testo rezultatai buvo laikomi statistiškai reikšmingais, jei p < = 0,05, reikšmingumo tendencija > = 0,05, bet < 0,1. Nepriklausomų imčių palyginimas buvo atliktas naudojant parametrinę dispersijos analizę (ANOVA) arba neparametrinį Dunno Kruskalo-Walliso testą. Daugkartinis mėginių palyginimas buvo atliktas taikant Dunno Kruskalo-Walliso testą poriniam palyginimui. Chi kvadrato ($\chi 2$) kriterijus buvo naudojamas įvertinti vardinės skalės ir lentelėse pateiktų dažninių charakteristikų tarpusavio priklausomybę. Priklausomai nuo imties dydžio, buvo naudojamas Fisherio tikslus arba Monte Karlo (mažiems mėginiams) ir asimptotinis $\chi 2$ testas.

Vaisiaus svoris buvo apskaičiuotas naudojant Hadlocko C lygties formulę. Apskaičiuota automatiškai naudojant sistemą *GE Healthcare Voluson E8*.

Visi doplerio parametrai buvo transformuoti į Z reikšmes pagal normatyvines nuorodas [102, 115].

REZULTATAI

Bendrosios tyrimo dalyvių charakteristikos, vaisiaus stebėjimo metodai ir perinataliniai rezultatai

Iš visų 158 į tyrimą įtrauktų dalyvių 126 iš viso 504 kartus apsilankiusios nėščiosios atitiko anksčiau aprašytus įtraukties kriterijus (žr. 1.1.). 32 pacientės buvo pašalintos iš tyrimo. Visos dalyvės buvo lietuvės, amžiaus vidurkis – 32,5 [29,0–35,3] metų (žr. 1 lentelę).

1 lentelė. Dalyvių charakteristikos. IQR – tarpkvartilis diapazonas, df – laisvės laipsnis, a - p reikšmė pagal nepriklausomų imčių Kruskalo-Walliso testą (angl. *Pairwise Comparisons of Group by Dunn's Test*), b - p reikšmė pagal Chi kvadrato testus.

Charakteristikos	**Grupės**				**p reikšmė**
	Visos tiriamosios (n = 126)	Didelės rizikos nėščiųjų be VAS (n = 56)	Didelės rizikos nėščiųjų su VAS (n = 53)	Mažos rizikos nėščiųjų (n = 17)	
Motinos vidutinis amžius metais [IQR]	32,5 [29,0–35,3]	33,0 [30,0–36,0] *	33,0 30,0–36,0] **	30,0 [28,0–31,0]*,**	*,**p < 0,05
Gimdymų skaičius					
Daugiakartės, n (%)	66 (52,4)	33 (58,9)	26 (49,1)	7 (41,2)	p = 0,358
Pirmą kartą gimdančios n (%)	60 (48)	22 (39)	27 (51)	10 (59)	p=0.358
Nėštumo patologijos ir gretutinės ligos, n (%)					
Preeklampsija	20 (16,8)	11 (19,6)	9 (19,6)	0 (0)	p = 0,135
Gestacinė hipertenzija	15 (11,9)	9 (16,1)	6 (11,3)	0 (0)	p = 0,207
Pirminė arterinė hipertenzija	10 (7,9)	8 (14,3)	2 (3,8)	0 (0)	p = 0,067
Koronovirusinė liga (COVID -19)	5 (4,0)	4 (7,1)	1 (1,9)	0 (0)	p = 0,352
Diabetas	4 (3,2)	3 (5,4)	1 (1,9)	0 (0)	> 0,999
Gestacinis diabetas	45 (35,7)	29 (51,8)	16 (30,2)	0 (0)	p = 0,242
Nėščiųjų cholestazė	11 (19,9)	9 (16,1)	2 (3,8)	0 (0)	> 0,999

Lyginant dalyvių grupes pagal nėštumo riziką, didelės rizikos nėščiųjų grupėse su diagnozuotu / nediagnozuotu VAS motinos amžiaus mediana [IQR] nesiskyrė (p > 0,05), o mažos rizikos grupėje motinos amžiaus mediana buvo statistiškai mažesnė (p < 0,05). Kalbant apie motinos amžių, didelės rizikos nėščiųjų grupė su diagnozuotu VAS ir didelės rizikos nėščiųjų grupė, kuriai nebūdingas VAS, buvo reikšmingai nevienodos, palyginti su mažos rizikos nėščiųjų grupe (žr. 4 lentelę). Didelės rizikos nėštumo grupės moterys buvo vyresnės, tačiau statistiškai reikšmingų skirtumų tarp šių trijų grupių daugiakarčių tiriamųjų nepastebėta (p > 0,5). Sąsajų tarp gretutinių ligų tipų tarp analizuojamų grupių nerasta. Be to, statistiškai reikšmingų skirtumų tarp

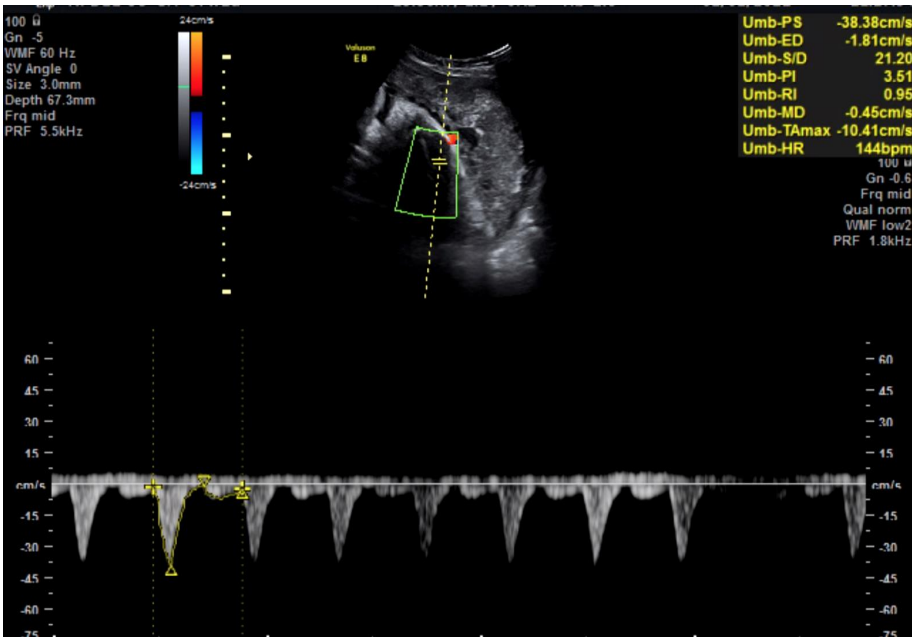
nenormalaus modifikuoto biofizinio profilio, oligohidramniono polihidramniono ar nereaktyvaus NST nebuvo rasta (žr. 2 lentelę).

2 lentelė. Antenatalinis vaisiaus stebėjimas.

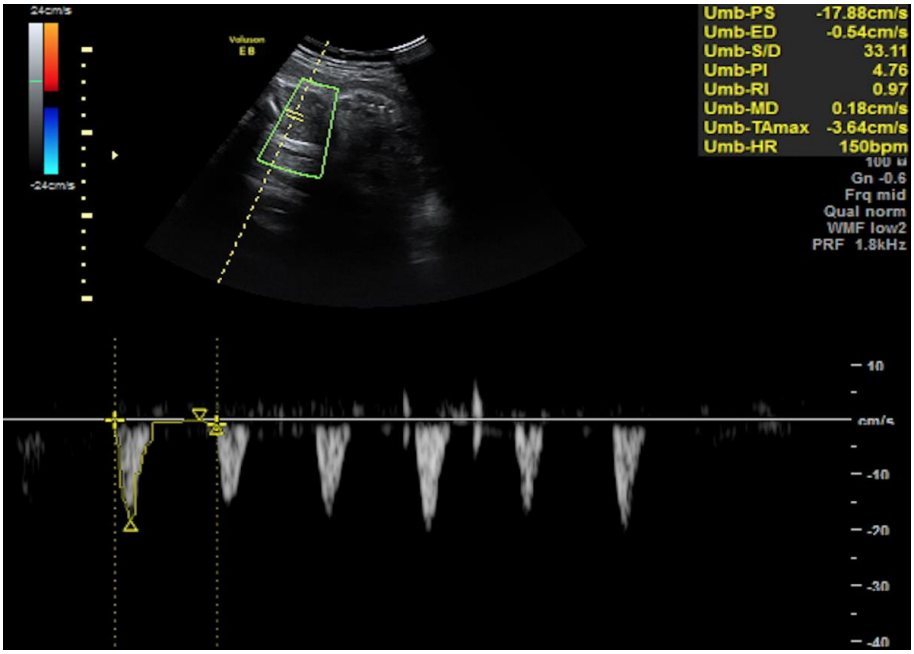
Patologinis vaisiaus būklės tyrimo rezultatas	Tiriamųjų skaičius n (proc.)				
	Visos tiriamosios (n=126)	Didelės rizikos nėščiosios be VAS (n=56)	Didelės rizikos nėščiosios su VAS (n=53)	Mažos rizikos nėščiosios (n=17)	P-reikšmė
Nenormalus modifikuotas biofizinis profilis	4 (3,2)	2 (3,6)	2 (3,8)	0 (0)	p=1,0
Oligohidramnionas	4 (3,2)	2 (3,6)	3 (3,8)	0 (0)	p=1,0
Polihidramnionas	3 (2,4)	3 (5,4)	0 (0%)	0 (0%)	p=0,203
Nereaktyvus NST	0 (0)	0 (0)	0 (0)	0 (0)	-

Mažos rizikos grupė

Nuo 33 iki 40 nėštumo savaitės visoms mažos rizikos nėštumo grupės dalyvėms nustatytas normalus vaisiaus BA-PI. Toliau pateiktame paveiksle pavaizduoti normalūs BA-PI parametrai 39 + 0 savaitę (žr. 7 pav., 8 pav.). Mažos rizikos nėštumo grupės dalyvių rezultatai parodė normalius išmatuotų kraujagyslių rodiklius, o naujagimiams statistiškai reikšmingų nepageidaujamų perinatalinių baigčių nenustatyta (žr. 5 lentelę). Mažos rizikos nėštumo grupės dalyvėms gimdymas prasidėjo savaime. Tik vieno gimdymo metu dėl vaisiaus hipoksijos buvo atliktas cezario pjūvis.

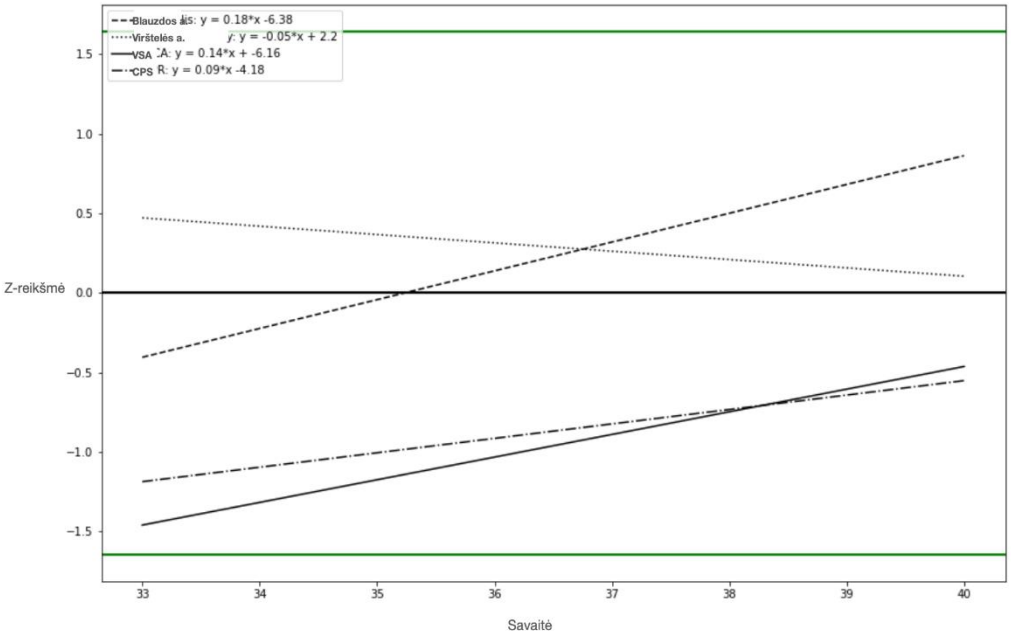


7 paveikslas. Blauzdos arterijos doplerio matavimas 39 sav. + 0 d., kai BA-PI normalus (matuojamas rankiniu būdu).



8 paveikslas. Doplerio matavimas 39 sav. + 0 d., kai BA-PI normalus (matuojamas rankiniu būdu).

Kaip parodyta 8 pav., visų analizuojamų arterijų PI ir CPS doplerio matavimų parametrai buvo transformuoti į Z reikšmes. 9 pav. matyti nuo 33 iki 40 nėštumo savaitės išlikę normalūs vaisiaus BA-PI parametrai. CPS, VA ir VSA Z reikšmės taip pat išliko normalios.



9 paveikslas. Mažos rizikos nėštumo doplerio matavimų parametrų Z reikšmių tendencijos tiriamuoju laikotarpiu: BA-PI, CPS, VSA-PI, VA-PI.

Didelės rizikos nėščiųjų be nustatyto vaisiaus augimo sulėtėjimo grupė

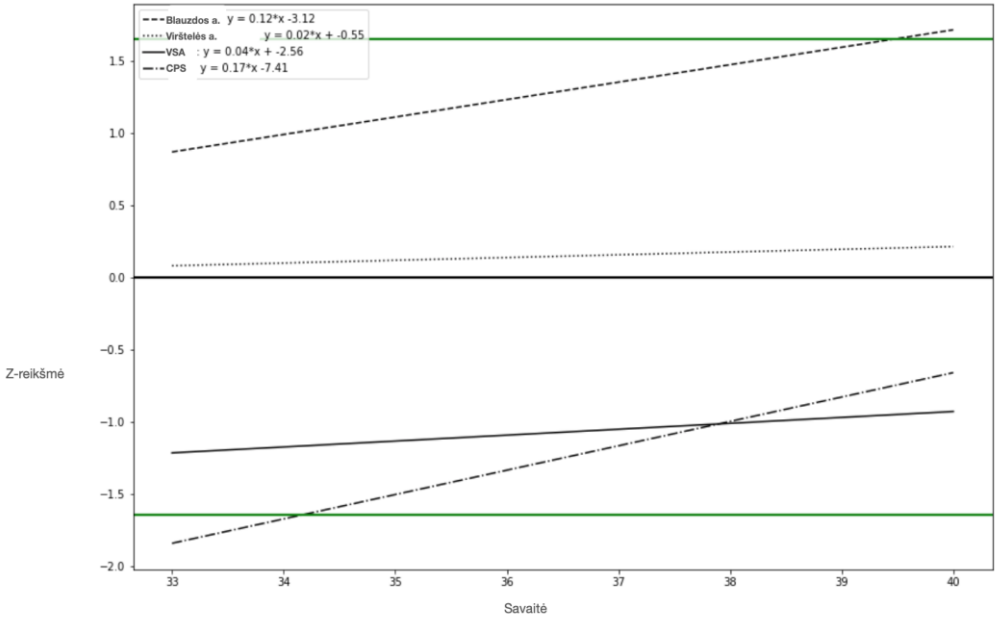
Didelės rizikos nėščiųjų be VAS grupės vaisiaus stebėjimo duomenų ir BA-PI normalių ir nenormalių doplerio PI reikšmių palyginimo rezultatai statistiškai reikšmingų rezultatų neparodė (žr. 3 lentelę). Be to, visų analizuojamų arterijų PI ir CPS doplerio matavimų parametrai buvo transformuoti į Z vertes. Todėl, kaip parodyta 11 paveiksle, vaisiaus BA-PI parametrai labiausiai nukrypo nuo normos 39–40 nėštumo savaitę ir buvo stebimas ryškiausias nenormalių reikšmių didėjimas. Tuo tarpu CPS, VA ir VSA, Z reikšmės išliko normalios.

Verta pabrėžti, kad, remiantis mūsų tyrimo išvadomis, BA-PI parametrai labiausiai keitėsi kartu su didėjančiu gestacijos amžiumi.

3 lentelė. Didelės rizikos nėščiųjų be VAS sutrikimų ir motinos gretutinių ligų palyginimas su normaliomis (BA-PI > 5 ir < 95 procentilių) ir nenormaliomis (> 95 procentilių) BA PI reikšmėmis paskutinę savaitę prieš gimdymą didelės rizikos nėščiųjų grupėje diagnozavus VAS, naudojant statistinius testus (*Pearsono Chi kvadrato testas, §tikslus Fisherio testas)

Charakteristikos	Grupės			
	Bendras dalyvių skaičius, N = 56 (n, (%))	**BA PI > 95 procentilės, N = 33 (n, (%))**	**BA PI > 5 ir < 95 proenti-lės, N = 23 (n, (%))**	**p reikšmė**
Pirminė arterinė hipertenzija§	8 (14,3 %)	4 (17,4 %)	4 (12,1 %)	0,704
Gestacinė hipertenzija§	9 (16,1 %)	3 (13,0%)	6 (18,2 %)	0,723
Diabetas§	3 (5,4 %)	2 (8,7%)	1 (3,0 %)	0,562
Gestacinis diabetas*	29 (51,8 %)	12 (52,2%)	17 (51,5 %)	0,961
Nėščiųjų cholestazė§	9 (16,1 %)	0 (0,0%)	9 (27,3 %)	0,007
Preeklampsija§	11 (19,6 %)	5 (21,7%)	6 (18,2 %)	0,746
Motinos koronavirusinė liga§ (COVID-19)	4 (7,1 %)	3 (13,0 %)	1 (3,0 %)	0,295

Daugelis mokslininkų nurodo, kad CRS yra patikimesnis vaisiaus būklės vertinimo tyrimas negu tiriant tik VSA-PI rodiklį. Tokia tendencija yra pastebima ir šioje tiriamųjų grupėje (žr. 10 paveikslą). Tirtų rodiklių rezultatus galėjo nulemti ir tai, kad tiriamųjų grupėse buvo keturios skirtingos patologijos.



10 paveikslas. Didelės rizikos nėščiosios be VAS. Doplerio parametrų Z reikšmės tiriamuoju laikotarpiu: BA-PI, CPS, VSA-PI, VA-PI.

Didelės rizikos nėščiųjų grupė su diagnozuotu vaisiaus augimo sulėtėjimu

Didelės rizikos nėščiųjų grupę su diagnozuotu VAS sudarė 53 moterys. Jos buvo palygintos atsižvelgiant į normalius ir nenormalius BA PI parametrus, išmatuotus likus savaitei iki gimdymo. Taikant vaisiaus stebėjimo priemones Didelės rizikos nėščiųjų grupėje su diagnozuotu VAS statistiškai reikšmingų rezultatų nenustatyta (žr. 4 lentelę). Visų moterų NST buvo normalus ir nė vienoje grupėje nebuvo rasta polihidramniono. Preeklampsijos atvejais nustatyta BA-PI parametrų statistinio reikšmingumo tendencija $p < 0,1$ (žr. 5 lentelę).

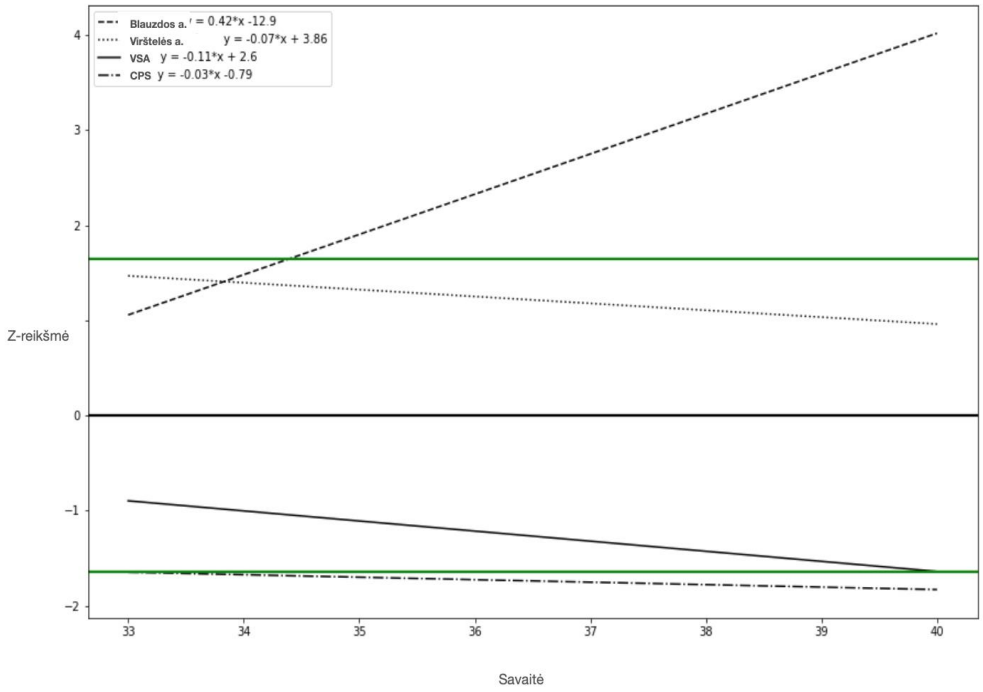
4 lentelė. Didelės rizikos nėščiųjų su diagnozuotu VAS grupėje patologijos ir motinos gretutinių ligų palyginimas su normaliomis (BA-PI > 5 ir < 95 procentilis) ir nenormaliomis (> 95 procentilis) BA PI reikšmėmis, gautomis likus savaitei iki gimdymo didelės rizikos nėščiųjų grupėje, naudojant statistinius testus (*tikslus Fisherio testas).

Charakteristikos	**Grupės**			**p reikšmė**
	Bendras tiriamųjų skaičius, N = 53 (n, (%))	**BA PI > 95 procentilis, N = 41 (n, (%))**	**BA-PI > 5 ir <95 procentilis), N = 12 (n, (%))**	
Pirminė arterinė hipertenzija*	2 (3,8 %)	2 (4,9 %)	0 (0,0 %)	> 0,999
Gestacinė hipertenzija*	6 (11,3 %)	6 (14,6 %)	0 (0,0 %)	0,317
Diabetas*	1 (1,9 %)	0 (0,0 %)	1 (8,3 %)	0,226
Gestacinis diabetas*	16 (30,2 %)	14 (34,1 %)	2 (16,7 %)	0,307
Intrahepatinė cholestazė*	2 (3,8 %)	2 (4,9 %)	0 (0,0 %)	> 0,999
Preeklampsija*	9 (17,0 %)	9 (22,0 %)	0 (0,0 %)	0,100
COVID-19 virus Nėščiosios koronavirusinė liga (COVID-19)	1 (1,9 %)	1 (2,4 %)	0 (0,0 %)	0,999

Detalesnei analizei visų tirtų arterijų PI ir CPS doplerio matavimų rodikliai buvo transformuoti į Z vertes. Iš 9 paveikslo matyti, kad vaisiaus blauzdos arterijos pulsacijos indekso rodikliai labiausiai nukrypo nuo normos 34–35 nėštumo savaitę ir parodė žymų nenormalių reikšmių didėjimą. Tuo tarpu CPS Z reikšmės taip pat nežymiai nukrypo nuo normos reikšmių, bet ne taip žymiai kaip blauzdos arterijos PI rodikliai. VSA Z reikšmės palaipsniui mažėjo, didėjant nėštumo trukmei. Tyrimo VSA parametrai patologines reikšmes pasiekė tik 39–40 nėštumo savaitę, o analizuojami VA arterijos parametrai išliko normalūs. Gautos išvados rodo, kad VA doplerometrija neturėjo jokios prognostinės vertės, nes liko normali. Šie radiniai sutampa su

kitų autorių gautais rezultatais, rodančiais, kad virkštelės arterijos doplerio parametrų reikšmės yra nepakankamas prognostinis vaisiaus būklės nustatymo rodiklis, kai nėštumas yra vėlyvas.

Analizė parodė, kad BA-PI parametrai daugiausiai kito didėjant nėštumo trukmei. Visgi nėra pakankamai tyrimų, patvirtinančių tokias išvadas. Dauguma mokslininkų nurodo, kad CPS yra patikimas vaisiaus būklės įvertinimo rodiklis, o VSA doplerometrija kaip vienintelis rodiklis nepatikimas. Ši tendencija matoma ir mūsų tyrime (žr. 11 paveikslą).



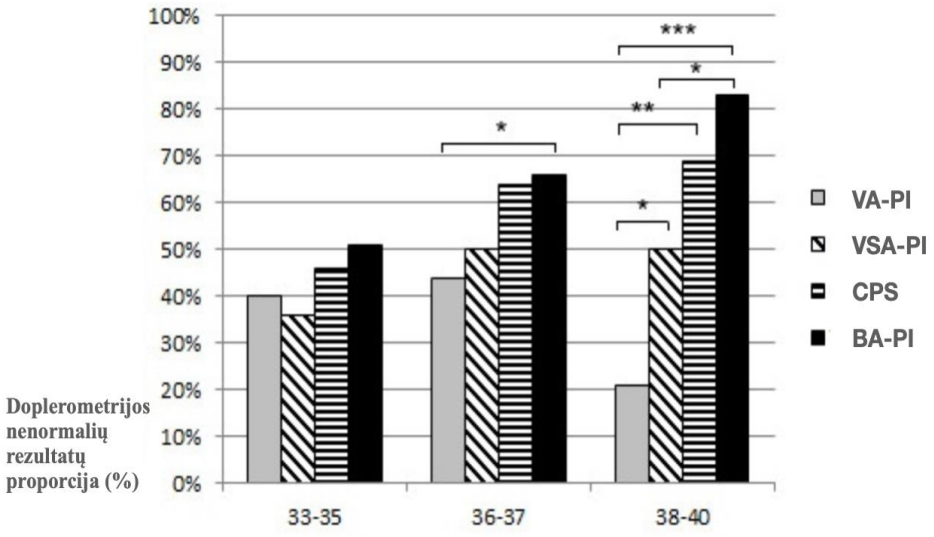
11 paveikslas. Didelės rizikos nėščiųjų grupė su diagnozuotu VAS. Doplerio parametrų Z reikšmės tiriamuoju laikotarpiu: BA-PI, CPS, VSA-PI, VA-PI.

Palyginus nenormalių PI ir CPS rodiklių proporcijas tarp arterijų Didelės rizikos nėščiųjų grupėje su diagnozuotu VAS nuo 33 iki 35 nėštumo savaitės, statistiškai reikšmingų visų arterijų PI pokyčių nepastebėta. Didelės rizikos nėščiųjų grupėje su diagnozuotu VAS nuo 36 iki 37 nėštumo savaitės reikšmingiausi patologiniai pokyčiai buvo nustatyti BA-PI, kurie taip pat buvo pastebėti didelės rizikos nėščiųjų grupėje su diagnozuotu VAS nuo 38 iki 40 nėštumo savaičių (žr. 6 lentelę). Antroji aptikta patologinių pokyčių dalis buvo CPS ir VSA-PI. Mažiausia nenormalių atvejų dalis nustatyta VA-PI.

6 lentelė. Didelės rizikos nėščiųjų grupė su diagnozuotu VAS. 33 ir 35, 36 ir 37, 38 nėštumo savaitę ir paskutinę savaitę prieš gimdymą matuotų virkštelės arterijos (BA-PI), VSA-PI, CPS ir BA-PI doplerio parametrų palyginimas (p – reikšmės: ***-p < 0,001, **-p < 0,01, *-p < 0,05).

	Grupė		
Kintamųjų (p reikšmių) palyginimas	33–35 nėštumo savaitės	36–37 nėštumo savaitės	38–40 nėštumo savaitės
VA-PI *vs* VSA-PI	0,727	0,619	**0,042**
VA-PI *vs* CPS	0,323	0,103	**0,002**
VA-PI *vs* BA-PI	0,246	**0,029**	**< 0,001**
CPS *vs* BA-PI	0,469	0,318	0,268
CPS *vs* BA-PI	0,192	0,184	**0,024**
CPS *vs* BA-PI	0,681	0,866	**0,306**

Iš 12 paveikslo matyti didėjanti nenormalių atvejų proporcija VA-PI, VSA-PI, CPS ir BA-PI. Statistiškai reikšmingas BA PI patologinių reikšmių didėjimas didelės rizikos nėščiųjų grupėje su diagnozuotu VAS nuo 36 iki 37 nėštumo savaitės ir nuo 38 iki 40 nėštumo savaitės.



12 paveikslas. Didelės rizikos nėščiųjų grupė su diagnozuotu VAS. Nenormalių VA-PI, VSA-PI, CPS ir BA-PI atvejų doplerometrijos rezultatų proporcija tarp 33 ir 35, 36 ir 37, 38 nėštumo savaitės ir paskutinio tyrimo metu prieš gimdymą. (p – reikšmės: ***-p < 0,001, **-p < 0,01, *-p < 0,05).

Gimdymo būdo analizė

Gimdymo būdo analizė tarp tiriamųjų grupių parodė statistiškai reikšmingus rezultatus lyginant 3 gimdymo būdus (gimdymo sužadinimas, CPO), savaiminis gimdymas). Statistiškai reikšmingi rezultatai buvo gauti lyginant savaiminio gimdymo dažnį mažos ir didelės rizikos su ir be VAS grupėse pagal spontaninį gimdymą, palyginti su didelės rizikos grupėmis su diagnozuotu VAS ir didelės rizikos grupėmis be VAS (žr. 9 lentelę).

9 lentelė. Tyrimo dalyvių gimdymo būdo palyginimas. Statistiniai testai (*Fišerio tikslus skaičiavimo duomenų imituotos p reikšmės testas (remiantis 2000 pakartojimų), §Pirsono chi kvadrato testas).

	Grupės				
Charakteristikos	**Visos tiramosios (n = 126)**	**Didelės rizikos nėščiųjų grupė su VAS (n = 56)**	**Didelės rizikos nėščiųjų grupė be VAS (n = 53)**	**Mažos rizikos nėščiųjų grupė (n = 17)**	**p reikšmė**
Gimdymo sužadinimas*, n (%)	34 (27)	14 (26,4)	20 (35,7)	0 (0)	p < 0,005
Planinė cezario pjūvio operacija*, n (%)	32 (25,4)	15 (28,3)	16 (28,6)	1 (5,9)	p = 0,131
Planinė cezario pjūvio operacija*, n (%)	16 (12,6)	8 (14,2)	8 (15,0)	0 (0)	p = 0,131
Savaiminis gimdymas§, n (%)	60 (476)	24 (45,3)	20 (35,7)	16 (94,1)	p < 0,001

Didelės rizikos nėščiųjų grupėje su diagnozuotu VAS gimdymo būdo skirtumai statistiškai nebuvo reikšmingi, tačiau tendencija buvo akivaizdi nenormalios BA grupėje. Grupės dalyvėms, palyginti su normalių BA grupe, buvo atlikta daugiau CPO, atitinkamai 29,3 ir 25 proc. (žr. 10 lentelę).

10 lentelė. Didelės rizikos nėščiųjų grupės su diagnozuotu VAS gimdymo būdo palyginimas su normaliais ir nenormaliais BA kraujotakos. Statistinis testas (*Fišerio tikslus skaičiavimo duomenų testas, imituotas p vertės (remiantis 2000 pakartojimų) §Pirsono chi kvadrato testas)

Charakteristikos	**Grupės**			**p reikšmė**
	Didelės rizikos nėščiųjų grupė su VAS (n = 53)	**Normalių BA-PI grupė (BA > 5 ir < 95 procentilis) (n = 12)**	**Nenormalių BA-PI grupė (TA>95 procentilis) (n = 41)**	
Gimdymo sužadinimas*, n (%)	14 (26,4)	4 (33,3)	10 (24,4)	p = 0,711
Cezario pjūvio operacija*, n (%)	15 (28,3)	3 (25,0)	12 (29,3)	p > 0,999
Savaiminis gimdymas§, n (%)	24 (45,3)	5 (41,7)	19 (46,3)	p = 0,775

Be to, panašios tendencijos buvo pastebėtos ir didelės rizikos nėščiųjų grupėje be VAS. Nors skirtumai nebuvo statistiškai reikšmingi, tendencija buvo pastebėta nenormalių kraujotakos tyrimų BA-PI grupėje. Šios grupės dalyvėms buvo atlikta daugiau cezario pjūvių operacijų (30,3 %), palyginti su normalių BA-PI grupės (26,1 %) (žr. 11 lentelę).

11 lentelė. Gimdymo būdo palyginimas didelės rizikos nėščiųjų be VAS grupėje su normaliais ir nenormaliais BA-PI atvejais. Statistiniai testai (*Pearson's Chi-squared test).

	Grupė			
Charakteristikos	**Didelės rizikos nėščiųjų grupė su VAS (n = 56)**	**Normalių BA-PI grupė (BA > 5 ir < 95 procentilis) (n = 33)**	**Nenormalių BA-PI grupė (TA>95 procentilis) (n = 23)**	**p reikšmė**
Gimdymo sužadinimas*, n (%)	20 (35,7)	11 (33,3)	9 (39,1)	p = 0,656
Cezario pjūvio operacija*, n (%)	16 (28,6)	10 (30,3)	6 (26,1)	p = 0,731
Savaiminis gimdymas*, n (%)	20 (35,7)	12 (36,4)	8 (34,8)	p = 0,903

12 lentelė. Cezario pjūvio operacija atlikta dėl vaisiaus hipoksijos.

	Grupės	
Cezario pjūvio operacija atlikta dėl vaisiaus hipoksijos (n=4)	**Normalių BA-PI tyrimo rezultatų grupė (BA>5 ir <95 procentilis)**	**Nenormalių BA-PI tyrimo rezultatų grupė (BA>95 procentilis)**
Didelės rizikos nėštumas esant VAS (n=2)	0	2 (50%)
Didelės rizikos nėštumas be VAS (n=2)	1 (25%)	1 (25%)

Tyrime taip pat išanalizuoti CPO, atliktų dėl vaisiaus hipoksijos, atvejai. Keturioms nėščiosioms CPO buvo atlikta dėl nustatytos ūminės vaisiaus hipoksijos. Iš viso 75 proc. moterų prieš gimdymą turėjo nenormalų BA-PI (žr. 12 lentelę).

Mekonijaus nustatymas amniono skystyje ir mekonijaus aspiracijos sindromo santykiai visose trijose grupėse reikšmingai nesiskyrė.

Nors naujagimių lyties skirtumai buvo nustatyti trijose grupėse, atvirkščiai, gimimo svorio kategorijoje statistiškai reikšmingi skirtumai buvo pastebėti visose grupėse ($p < 0,05$), o mažiausias gimimo svoris – 2371,7 (409,2) gramo – užfiksuotas didelės rizikos grupėje su diagnozuotu VAS. Be to, didelės rizikos grupė su diagnozuotu VAS apėmė naujagimius, kurių numatomas vaisiaus svoris buvo < 5 ir < 10 procentilis. Be to, naujagimio vertinimas pagal Apgar skalę balais po 5 minučių buvo daug mažesnis didelės rizikos grupėje su diagnozuotu VAS, 9,5 [9,0–10,0], palyginti su didelės rizikos grupėmis be VAS, 10,0 [9,0–10,0] ir mažos rizikos grupėje 10,0 [10,0–10,0] ($p < 0,028$). Tačiau kitose grupėse skirtumų nerasta. Metabolinė acidozė buvo diagnozuota 0,8 proc. naujagimių, nes virkštelės arterijos pH buvo mažesnis nei 7. Tačiau VA pH skirtingose grupėse labai skyrėsi.

13 lentelė. Perinatalinės baigtys. Statistiniai metodai (IQR – tarpkvartilis diapazonas, df – laisvės laipsnis, M – vidurkis, SD – standartinis nuokrypis: ap vertė pagal nepriklausomų imčių Kruskal-Wallis testą (porinis grupės palyginimas pagal Dunno testą); bp vertė Chi kvadrato testais; cp vertė pagal vienpusį ANOVA (porinis grupės palyginimas pagal Bonferroni testą)

	Grupės				
Charakteristikos	**Visos tiriamosios (n = 126)**	**Didelės rizikos nėščiųjų grupė be VAS (n = 56)**	**Didelės rizikos nėščiųjų grupė su VAS (n = 53)**	**Mažos rizikos nėščiųjų grupė (n = 17)**	**p reikšmė**
Nėštumo trukmės mediana gimdymo metu (sav.) Median [IQR]	38,5 [37,0–39,0]	39,0 [38,0–39,0] *	38,0 [37,0–39,0]**	40,0 [39,0–40,0] *,**	p < 0,001; *,**p < 0,05
Mekonijus vaisiaus vandenyse, n (%)	4 (3,2)	2 (3,6)	2 (3,8)	0 (0%)	p = 1,0
Mekonijaus aspiracijos sindromas, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Naujagimio lytis, n (%) Vyriška Moteriška	61 (48,4) 65 (51,6)	28 (50,0) 28(50,0)	22 (41,5) 31 (58,5)	11 (64,7) 6 (35,3)	p = 0,238
Gimimo svoris (g), M(SD)	2956,3 (684,7)	3304,6 (538,4)*,**	2371,7 (409,2) *,***	3631,5 (284,8) **,***	p < 0,001[b]; *,**,***p < 0,05

Gimimo svoris <5 procentilis, n (%)	32 (25,3)	0 (0,0) *	32 (100)*,**	0 (0) **	p < 0,001[a]; *,**p < 0,05
Gimimo svoris <10 procentilis, n (%)	53 (42)	0 (0,0) *	53 (100) *,**	0 (0) **	p < 0,001[a]; *,**p < 0,05
VA pH mediana [IQR]	7,29 [7,23–7,34]	7,29 [7,2–7,33] *	7,33 [7,29–7,36] *,**	7,28 [7,21–7,32] **	p = 0,026[a]; *,**p < 0,05
VA pH < 7,35, n (%)	100 (80,0)	44 (80,0)	40 (75,5)	16 (94,1)	p = 0,247[b]
VA pH < 7,2, n (%)	22 (17,6)	14 (25,5)	5 (9,4)	3 (17,6)	p = 0,092[b]
VA pH < 7, n (%)	1 (0,8)	1 (1,8)	0 (0)	0 (0)	p = 1,0[b]
Apgar balai 5 min. mediana [IQR]	10.0 [9,0–10,0]	10,0 [9,0–10,0]	9,5 [9,0–10,0] *	10,0 [10,0–10,0] *	p = 0,028[a]; *p < 0.05
Kvėpuojamoji terapija, n (%)	11 (8,7)	5 (8,9)	5 (9,4)	1 (5,9)	p = 1,0[b]
Naujagimių gelta, n (%)	26 (20,6)	10 (17,9)	15 (28,3)	1 (5,9)	p = 0,114[b]
Naujagimių hipoglikemija, n (%)	9 (7,3)	2 (3,6)	6 (4,8)	1 (5,9)	p = 0,271[b]

Palyginus visas tris naujagimių grupes, nustatytas statistiškai reikšmingas naujagimių gestacijos savaičių skirtumas. Didelės rizikos nėščiųjų grupėje be VAS ir didelės rizikos nėščiųjų grupėje su nustatytu VAS nėštumo trukmė buvo daug mažesnė, palyginti su trečiąja mažos rizikos nėščiųjų grupe (žr. 13 lentelę).

Vaisiaus lytis, vidutinės nėštumo trukmės, naujagimio svorio mediana, vaisiaus svoris < 5 procentilės ir < 10 procentilis statistiškai reikšmingų skirtumų nerodė. Iš viso patologinės BA PI doplerometrijos grupėje kvėpuojamoji terapija buvo reikalinga 12,2 proc. naujagimių, jie sudarė 8,4 proc. visų atvejų. Priešingai, kai BA PI parametras buvo normalus, kvėpuojamosios terapijos nereikėjo. Nėščiųjų grupėje, kurių doplerometrijos rezultatai BA PI > 95 procentilis, kvėpuojamoji terapija buvo pritaikyta 5 naujagimiams, o normalių BA-PI grupėje – 0 naujagimių. Nors kvėpuojamoji terapija buvo taikoma net 5 naujagimiams iš 53 atvejų, kurių BA PI > 95 procentilis, statistinių metodų, leidžiančių patvirtinti 0 ir 5 imtį, nėra.

Naujagimių geltos dažnis grupėse statistiškai reikšmingai nesiskyrė. Moterų, kurių BA PI > 95 procentilio, naujagimiams buvo diagnozuota gelta 29,3 proc., tuo tarpu moterų, kurių BA kraujotaka buvo normali, gelta sirgo 25 proc. naujagimių. Panašios tendencijos buvo pastebimos hipoglikemija sergančių naujagimių grupėje. Penkiems naujagimiams šis sutrikimas diagnozuotas patologinės BA PI grupėje, o nrmalios BA PI grupėje buvo tik vienas naujagimis (žr. 14 lentelę). Nors šios tendencijos neatskleidė statistinio reikšmingumo, jos leidžia daryti prielaidą apie statistinį reikšmingumą, kuris gali atsirasti, jei imtis bus padidinta.

14 lentelė. Perinatalinių baigčių palyginimas normalių (BA-PI > 5 ir < 95 procentilis) ir nenormalių (PI > 95 procentilis) PI reikšmių grupėse, kai BA PI buvo užregistruotas paskutinę savaitę prieš gimdymą didelės rizikos nėščiųjų grupėje su nustatytu vaisiaus augimo sulėtėjimu, naudojant statistinius testus (*tikslus Fisherio testas, ±3 Wilcoxon rank sum testas, §Wilcoxon rank sum exact test)

Charakteristikos	**Bendras tiriamųjų skaičius, N = 53**	**BA PI > 95 procentilis, N = 41**	**BA-PI > 5 ir < 95 procentilis, N = 12**	**p reikšmė**
Vaisiaus svorio procentilis* < 5	33 (62,3 %)	24 (58,5 %)	9 (75,0 %)	0,500

Vaisiaus svorio procentilis* < 10	53 (100 %)	42 (79,2 %)	11 (20,8 %)	0,665
Oligohidramnionas* AFI < 5	2 (3,8%)	2 (4,9 %)	0 (0,0 %)	> 0,999
Nenormalus modifikuotas biofizinis profilis*	2 (3,8 %)	2 (4,9 %)	0 (0,0 %)	> 0,999
Mekoniumas vaisiaus vandenyse*	2 (3,8 %)	1 (2,4 %)	1 (8,3 %)	0,405
Mekoniumo aspiracijos sindromas	0	0	0	-
VA pH± mediana (IQR)	7,33 (7,29, 7,35)	7,33 (7,30, 7,35)	7,31 (7,28, 7,37)	0,725
Kvėpuojamoji terapija*	5 (9,4 %)	5 (12,2 %)	0 (0,0 %)	0,577
Naujagimių gelta jaundice*	15 (28,3 %)	12 (29,3 %)	3 (25,0 %)	> 0,999
Naujagimio hipoglikemija*	6 (11,3 %)	5 (12,2 %)	1 (8,3 %)	> 0,999
Apgar balai±, 1 min. Mediana (IQR)	9 (8,00, 9,00)	9 (8,00, 9,00)	9 (9,00, 9,00)	0,500
Apgar balai±, 5 min. Mediana (IQR)	9,5 (9,00, 10,00)	9 (9,00, 10,00)	10 (9,00, 10,00)	0,487
Vaisiaus svoris§ Z balai Mediana (IQR)	-1,98 (-2,87, -1,42)	-1,92 (-2,88, -1,39)	-2,12 (-2,29, -1,47)	0,978
Gimimo ūgis±, cm Mediana (IQR)	48 (46,0, 50,0)	47,5 (45,8, 50,0)	48 (47,8, 50,0)	0,352
VA pH < 7	0 (0,0 %)	0 (0,0 %)	0 (0,0 %)	
VA pH* < 7,2	5 (9,4 %)	5 (12,2 %)	0 (0,0 %)	0,577
VA pH* < 7,35	37 (69,8 %)	29 (70,7 %)	8 (66,7 %)	> 0,999

Didelės rizikos nėščiųjų be diagnozuoto VAS perinatalinių baigčių, normalių ir nenormalių BA PI reikšmių grupėse, statistiškai reikšmingai nesiskyrė (žr. 15 lentelę).

15 lentelė. Perinatalinių baigčių palyginimas normalių (BA-PI > 5 ir < 95 procentilis) ir nenormalių (PI > 95 procentilis) PI verčių grupėse, kai BA PI buvo užregistruotas paskutinę savaitę prieš gimdymą didelės rizikos nėščiųjų grupėje be vaisiaus augimo sulėtėjimo, naudojant statistinius testus (*Fisher's exact test, §Wilcoxon rank sum test).

Charakteristikos	Bendras tiriamųjų skaičius, N = 56	BA PI > 95 procentilis, N =33	BA PI > 5 ir <9 5 procentilis, N = 23	p reikšmė
Gimimo savaitė§ Mediana (IQR)	39,00 (38,00, 39,00)	39,00 (37,50, 39,00)	39,00 (38,00, 39,00)	0,731
Naujagimio svoris§, g Mediana (IQR)	3,265 (2,950, 3,624)	3,180 (2,915, 3,395)	3,430 (3,170, 3,640)	0,127
Mekoniumas*	2 (3,6 %)	0 (0,0 %)	2 (6,1 %)	0,507
Virkštelės arterijos pH§ Mediana (IQR)	7,30 (7,20, 7,33)	7,31 (7,23, 7,34)	7,27 (7,20, 7,33)	0,293
Kvėpuojamoji terapija*	5 (8,9 %)	1 (4,3 %)	4 (12,1 %)	0,639
Naujagimių gelta*	10 (17,9 %)	5 (21,7 %)	5 (15,2 %)	0,725
Naujagimių hipoglikemija*	2 (3,6%)	1 (4,3%)	1 (3,0%)	> 0,999
Apgar balai§, 1 min. Mediana (IQR)	9 (9,00, 9,00)	9 (9,00, 9,00)	9 (9,00, 9,00)	0,490
Apgar balai§, 5 min. Mediana (IQR)	10 (9,00, 10,00)	10 (9,25, 10,00)	10 (9,00, 10,00)	0,897
VA pH* < 7	1 (1,8 %)	0 (0,0 %)	1 (3,0 %)	> 0,999
VA pH* < 7,2	12 (21,4 %)	5 (21,7 %)	7 (21,2 %)	> 0,999
VA pH* < 7,35	44 (78,6%)	18 (78,3%)	26 (78,8%)	> 0,999

REZULTATŲ APTARIMAS

Atliktas tyrimas yra pirmasis tyrimas, kurio metu buvo ištirtos ir aprašytos mažos ir didelės rizikos nėščiųjų vaisiaus periferinės BA PI doplerometrijos charakteristikos ir stebėjimo tyrimo dinamika nuo 33 iki 40 nėštumo savaitės ir gauti rezultatai palyginti su perinatalinėmis baigtimis.

Tyrimas neparodė žymios vertės stebint mažos rizikos nėščiąsias. Mažos rizikos nėščiųjų grupėje nebuvo nustatyta nenormalių BA PI rodiklių

pakitimų. Pakitimai neužfiksuoti viso tyrimo metu, taip pat nebuvo blogų perinatalinių baigčių. Priešingai, BA parametrų PI didelės rizikos nėščiųjų grupėje grupėse su diagnozuotu / nediagnozuotu VAS rodė žymių pokyčių. Taip pat buvo įvertinta BA PI rodiklio reikšmė prognozuojant blogėjančią vaisiaus būklę didelės rizikos nėščiosioms. Mūsų tyrimo rezultatai parodė, kad šis metodas gali pagelbėti stebėti vaisiaus būklę klinikinėje praktikoje. Atliktas tyrimas rodo netolygų pasiskirstymą vertinant gimdymo būdą, galėjusį turėti įtakos perinatalinėms baigtims. Galima daryti prielaidą, kad jei tyrime būtų analizuojamas tik vienas konkretus gimdymo būdas, rezultatai būtų tikslesni. Tokį tyrimą būtų galima atlikti ateityje.

Šio tyrimo rezultatai parodė, kad BA PI didelės rizikos nėščiųjų grupėje su nustatytu VAS ankščiausiai buvo registruojamas rodiklių artėjimas link patologinės reikšmės palyginti su kitų kraujagyslių rodikliais. Taip pat išryškėjo pokyčiai vaisiaus kraujotakoje palyginti su didelės rizikos nėščiųjų grupe be VAS ir mažos rizikos nėščiųjų grupe. Šis BA PI padidėjimas yra susijęs su didėjančiu vaisiaus periferinių arterijų susiaurėjimu, kaip galimos adaptacijos beprasidedant vaisiaus kraujotakos centralizacijai.

Tyrimas rodo, kad periferinių arterijų doplerometrija geriau atspindi vaisiaus būklę didelės rizikos nėščiųjų grupėje su nustatytu vėlyvuoju VAS. Taigi antenatalinė patikra įtraukiant šį metodą kartu su kitais vaisiaus stebėjimo metodais trečiuoju nėštumo trečdaliu greičiausiai turėtų didelę teigiamą įtaką perinataliniams rezultatams. Vaisiaus gimimui tinkamiausias nėštumo užbaigimo laikas didelės rizikos nėščiosioms visada kėlė didžiulį klinikinį iššūkį.

Atlikto tyrimo perinatalinių baigčių palyginimas parodė blauzdos kraujotakos tyrimą kaip papildomą priemonę, svarbią stebint nėštumą trečiuoju nėštumo trečdaliu iki gimdymo. Mūsų tyrimo rezultatai neparodė šio metodo žymaus pranašumo palyginti su dažniausiai naudojamais metodais. Didelės rizikos nėščiųjų grupėje, kai nediagnozuotas VAS, buvo pastebėti BA-PI kitimai artėjant gimdymo terimui. Tai gali būti naudingas papildomas tyrimo metodas didelės rizikos nėščiųjų be VAS vaisiaus būklės stebėsenai.
Mažos rizikos nėščiųjų vaisiaus BA-PI doplerometrijos rodikliai išliko ribose stebėto laikotarpio metu, todėl manome, kad šis tyrimas mažos rizikos nėščiosioms netikslingas.

Literatūroje aprašomi panašūs ankstesni tyrimai rodo, kad didelės rizikos nėščiųjų su nustatytu VAS nuo 36 nėštumo savaitės blauzdos arterijos PI didėja [19]. Kaip rodo 23–42 nėšumo savaičių vaisių tyrimas, BA PI stebėjimas leidžia anksčiausiai aptikti vaisiaus kraujotakos pokyčius, galimai dėl sąlygotos centralizacijos [26].

Disertacijoje parodoma, kad didelės rizikos nėščiųjų vaisiaus periferinės BA-PI doplerometrijos stebėjimo metodo pasirinkimas gali papildyti dabartinius vaisiaus stebėjimo metodus stebint didelės rizikos nėščiąsias su diagnozuotu vėlyvuoju VAS. Tai gali pagelbėti siekiant tiksliau įvertinti intrauterininę vaisiaus būklę, planuojant gimdymo laiką.

Atliktas tyrimas unikalus tuo, kad buvo tirta vaisiaus blauzdos arterijos kraujotaka. Dažniausiai vaisiaus intrauterinės būklės tyrimai yra skirti tik centrinėms, o ne periferinėms kraujagyslėms tirti. Toks tyrimo metodas gali parodyti vieną iš ankstesnių blogėjančios vaisiaus būklės požymių, palyginti su kitais stebėjimo tyrimais, skirtais vaisiaus būklei stebėti. Didžiausia vertė pastebėta didelės rizikos nėščiosioms su nustatytu VAS.

TYRIMO PRIVALUMAI IR TĘSTINUMAS

Pagrindinis tyrimo privalumas yra tyrimo metodikos unikalumas ir sutelktas dėmesys į iki šiol mažai tirtą periferinę vaisiaus kraujotaką. Mūsų duomenimis, mokslinėje literatūroje nebuvo atlikta palyginamoji analizė BA PI rodiklių ir kitų dažniausiai naudojamų vaisiaus būklės vertinimo metodų bei perinatalinių baigčių. Taip pat svarbu paminėti, kad matavimus naudodamas tą pačią įrangą atliko vienas tyrėjas. Be to, priešingai nei kituose tyrimuose, čia buvo analizuotos tiek patologinės, tiek normalios vertės, leidžiančios geriau interpretuoti rezultatus.

Tyrimas ateityje galėtų būti plečiamas su dar didesne dalyvių imtimi, atliekant daugiacentrį tyrimą, kad vėliau BA PI doplerometrijos metodas galėtų būti patvirtintas ir naudojamas akušerinėse rekomendacijose, kaip antenatalinės vaisiaus būklės vertinimui.

Manytina, kad tai pirmasis tęstinis tyrimas, kurio vidutinis stebėjimo laikotarpis penkios savaitės, kai buvo registruota doplerio parametrų kitimoas centrinėse ir periferinėse arterijose. Be to, buvo sutelktas dėmesys į perinatalines baigtis.

TYRIMO TRŪKUMAI

Apibendrinat tyrimą, galima paminėti keletą jo trūkumų. Visų pirma, ne visas tiriamąsias buvo galima įtraukti į analizę, nes trūko kai kurių kintamųjų duomenų. Be to, tyrimas buvo atliekamas pasaulinės Covid-19 pandemijos metu, todėl buvo laikomasi vyriausybės nustatytų apribojimų sveikatos priežiūros įstaigose: gydytojų laikas buvo ribojamas tiek bendraujant su pacientais (per nuotolį ir tiesiogiai), tiek juos apžiūrint ar tiriant. Mažos rizikos

nėščiųjų imtis buvo didžiausia įmanoma pagal tuometines galimybes. Negyvagimių ar naujagimių, kuriems buvo nustatyta sunki asfiksija, registruota nebuvo. Didesnės imties ir su blogomis perinatalinėmis baigtimis tolesni didelės rizikos nėščiųjų tyrimai diagnozavus / nediagnozavus VAS turėtų būti daugiafunkciai ir padėti padaryti tinkamas išvadas, teikti rekomendacijas, kaip stebėti didelės rizikos nėštumą diagnozavus vėlyvą VAS ir parinkti tinkamą gimdymo laiką dėl blogėjančios vaisiaus būklės.

IŠVADOS

1. Periferinės vaisiaus kraujotakos doplerometrijos tyrimas – vaisiaus blauzdos arterijos pulsacijos indekso matavimas – mažos rizikos nėštumo metu neturi papildomos reikšmės perinatalinėms baigtims. Mažos rizikos nėščiųjų grupėje nebuvo nustatyta nenormalių vaisiaus blauzdos arterijos, vidurinės smegenų arterijos, virkštelės arterijos doplerometrijos pulsacijos indeksų ir cerebroplacentinio santykio reikšmių.
2. Didelės rizikos nėštumo metu (hipertenzinės būklės, diabetas, intrahepatinė nėščiųjų cholestazė, COVID-19 infekcija) nenustačius vaisiaus augimo sulėtėjimo vaisiaus blauzdos arterijos pulsacijos indekso matavimas gali turėti papildomos prognostinės reikšmės perinatalinėms baigtims artėjant gimdymo terminui. Vaisiaus blauzdos arterijos pulsacijos indekso parametrai labiausiai nukrypo nuo normos 39–40 nėštumo savaitę, tuo tarpu vidurinės smegenų arterijos, virkštelės arterijos doplerometrijos pulsacijos indeksų ir cerebroplacentinio santykio Z reikšmės išliko normalios.
3. Didelės rizikos nėštumo (hipertenzinės būklės, diabetas, intrahepatinė nėščiųjų cholestazė, COVID-19 infekcija) metu diagnozavus vaisiaus augimo sulėtėjimą periferinės kraujotakos doplerometrijos tyrimas turi papildomos prognostinės reikšmės perinatalinėms baigtims, vertinant patologinius blauzdos arterijos rodiklius, kai pulsacijos indekso vertė virš 95 procentilio nuo 35 nėštumo savaitės.

PRAKTINĖS REKOMENDACIJOS

1. Vaisiaus blauzdos arterijos pulsacijos indekso doplerio matavimas nerekomenduojamas stebint normalų nėštumą. Atliktame tyrime jis neparodė nenormalių pakitimų, be to, neapmokytiems darbuotojams nėra lengva juo naudotis.

2. Didelės rizikos nėščiosioms su diagnozuotu vėlyvuoju vaisiaus augimo sulėtėjimu rekomenduojama atlikti vaisiaus blauzdos arterijos

doplerometriją, kaip papildomą metodą, vaisiaus būklei įvertinti nuo 35 nėštumo savaičių. Nustačius patologinę vertę (BA PI virš 95 procentilio), rekomenduojamas intensyvesnis vaisiaus būklės stebėjimas dėl nėštumo užbaigimo laiko.

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LIST OF PUBLICATIONS AND PRESENTATIONS

This dissertation is based on the research results presented in the following articles:

1. **Norvilaitė, K.,** Ramašauskaitė, D., Bartkevičienė, D., Šliachtenko, A., Kurmanavičius, J. Fetal Tibial Artery Doppler in Late IUGR Fetuses: A Longitudinal Study. *J. Clin. Med.* **2023**, *12*, 82. https://doi.org/10.3390/jcm12010082

2. **Norvilaitė K**, Ramašauskaitė D, Bartkevičienė D, Žaliūnas B, Kurmanavičius J. Doppler Ultrasonography of the Fetal Tibial Artery in High-Risk Pregnancy and Its Value in Predicting and Monitoring Fetal Hypoxia in IUGR Fetuses. Medicina (Kaunas). 2021 Sep 29;57(10):1036. doi: 10.3390/medicina57101036. PMID: 34684073; PMCID: PMC8538259.

Publications related to the content but not directly included in this dissertation:

1. Žaliūnas B, Jakaitė V, Kurmanavičius J, Bartkevičienė D, **Norvilaitė K**, Passerini K. Reference values of fetal ultrasound biometry: results of a prospective cohort study in Lithuania. Arch Gynecol Obstet. 2022 Nov;306(5):1503-1517. doi: 10.1007/s00404-022-06437-z. Epub 2022 Feb 27. PMID: 35220480.

2. Serapinas D, Boreikaitė E, Bartkevičiūtė A, **Norvilaitė K**, Narbekovas A, Bartkevičienė D. The Level of Free Fetal DNA as Precise Noninvasive Marker for Chromosomal Aneuploidies: First Results from BALTIC Region. Medicina (Kaunas). 2020 Oct 30;56(11):579. doi: 10.3390/medicina56110579. PMID: 33143018; PMCID: PMC7694133.

3. **Norvilaite K**, Kezeviciute M, Ramasauskaite D, Arlauskiene A, Bartkeviciene D, Uvarovas V. Postpartum pubic symphysis diastasis-conservative and surgical treatment methods, incidence of complications: Two case reports and a review of the literature. World J Clin Cases. 2020 Jan 6;8(1):110-119. doi: 10.12998/wjcc.v8.i1.110. PMID: 31970176; PMCID: PMC6962077.

Presentations:

1. “Abnormal tibial artery doppler in a patient with pre-eclampsia and IUGR fetus. Case report” presented in “American College of Obstetricians and

Gynecologists Annual Clinical Scientific Meeting; San Diego, California, 6-8 May 2022.

2. “Longitudinal doppler velocimetry in fetal tibial, umbilical, middle cerebral arteries and the cerebroplacental ratio in later growth-restricted fetuses” was presented in “Joint International Meeting: 22nd EAA Congress, 15th ISGA Congress, 5th International Conference of Evolutionary Medicine”, Vilnius, Lithuania, 24-27 August 2022.

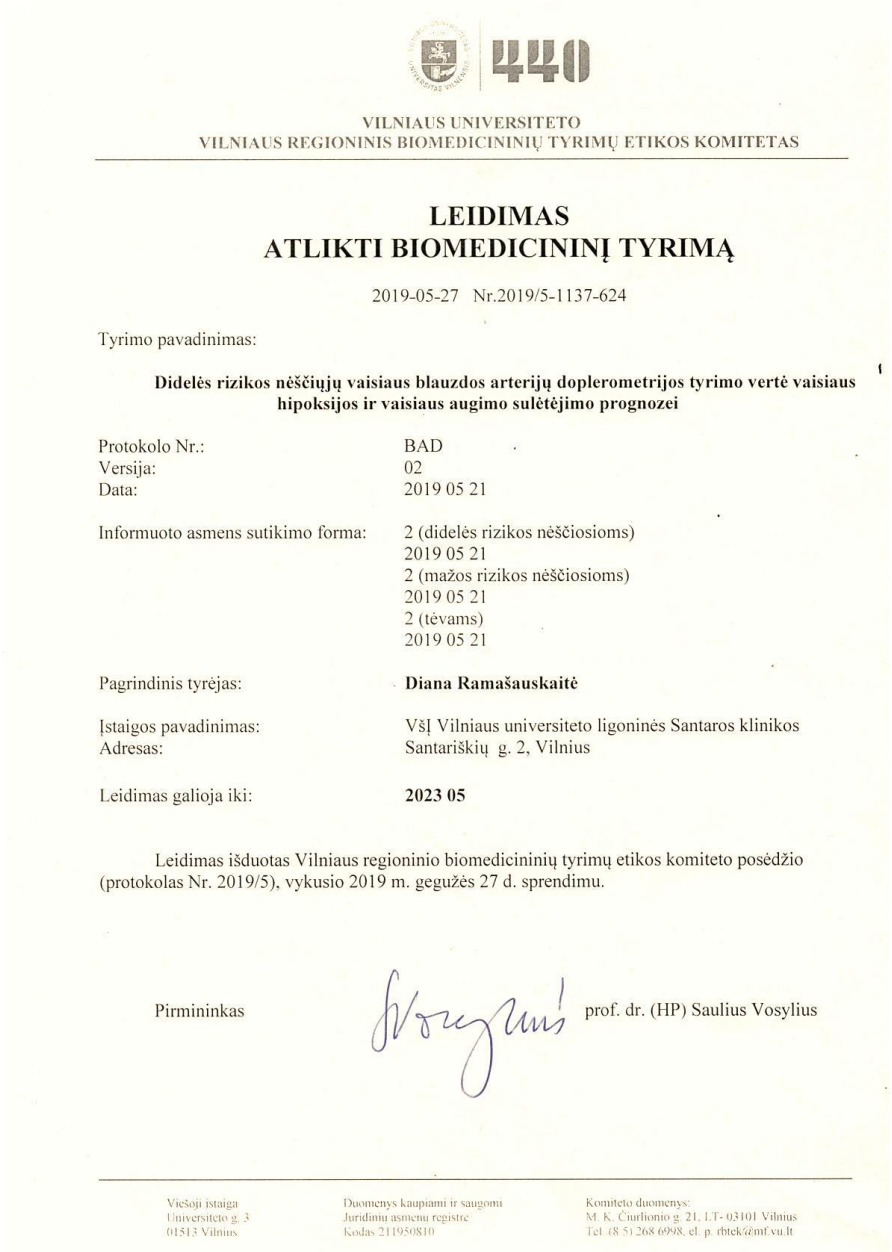
3. “Abnormal tibial artery in IUGR fetus. Case report” was presented in "XXIII FIGO World Congress of Gynecology and Obstetrics Congress” 24 - 29 October 2021, Sydney, Australia.

4. ”Abnormal tibial artery Dopplerometry of a growth restricted fetus with a genetic syndrome: A case report“ was presented in “29 World Congress on Ultrasound in Obstetrics and Gynecology, ISUOG”, 12-16 October 2019, Berlin, Germany.

Annex 1. Fitted centiles for the pulsatility index of the anterior tibial artery.

Week of gestation	*5th centile*	*50th centile*	*95th centile*
23.00	2.31	3.29	4.37
24.00	2.30	3.30	4.40
25.00	2.30	3.31	4.44
26.00	2.31	3.33	4.48
27.00	2.31	3.35	4.52
28.00	2.32	3.37	4.56
29.00	2.33	3.40	4.61
30.00	2.34	3.43	4.66
31.00	2.36	3.47	4.72
32.00	2.38	3.51	4.78
33.00	2.40	3.55	4.85
34.00	2.43	3.59	4.92
35.00	2.46	3.64	4.99
36.00	2.49	3.69	5.07
37.00	2.52	3.75	5.15
38.00	2.56	3.81	5.24
39.00	2.60	3.88	5.33
40.00	2.65	3.94	5.43
41.00	2.70	4.01	5.53
42.00	2.75	4.09	5.64

Annex 2. Ethical approval.



VILNIAUS UNIVERSITETO
VILNIAUS REGIONINIS BIOMEDICININIŲ TYRIMŲ ETIKOS KOMITETAS

LEIDIMAS
ATLIKTI BIOMEDICININĮ TYRIMĄ

2019-05-27 Nr.2019/5-1137-624

Tyrimo pavadinimas:

Didelės rizikos nėščiųjų vaisiaus blauzdos arterijų doplerometrijos tyrimo vertė vaisiaus hipoksijos ir vaisiaus augimo sulėtėjimo prognozei

Protokolo Nr.:	BAD
Versija:	02
Data:	2019 05 21
Informuoto asmens sutikimo forma:	2 (didelės rizikos nėščiosioms) 2019 05 21 2 (mažos rizikos nėščiosioms) 2019 05 21 2 (tėvams) 2019 05 21
Pagrindinis tyrėjas:	**Diana Ramašauskaitė**
Įstaigos pavadinimas: Adresas:	VšĮ Vilniaus universiteto ligoninės Santaros klinikos Santariškių g. 2, Vilnius
Leidimas galioja iki:	**2023 05**

Leidimas išduotas Vilniaus regioninio biomedicininių tyrimų etikos komiteto posėdžio (protokolas Nr. 2019/5), vykusio 2019 m. gegužės 27 d. sprendimu.

Pirmininkas prof. dr. (HP) Saulius Vosylius

Viešoji įstaiga
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Duomenys kaupiami ir saugomi
Juridinių asmenų registre
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ACKNOWLEDGEMENTS

Undertaking this dissertation has been a truly life-changing experience for me, and it would not have been possible to do without the support and guidance that I received from many people.

I would like to express my sincere gratitude to my scientific supervisor Prof. Dr. Diana Ramašauskaitė for valuable guidance and counceling through this dissertation, sincere and selfless support, prompt and useful advice during my research.

A depth gratitude is also owned to my scientific consultant Prof. Dr. Juozas Kurmanavičius for pointing me toward a relevant research idea and insights, for his global scientific expertise and knowledge, selfless support and kindness.

I would like to take this opportunity to express my immense gratitude to dear Mom and family, and all those who had given their invaluable support and assistance.

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