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MODERN APPROACHES TO EARLY DIAGNOSIS OF FETAL GROWTH RESTRICTION

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Abstract: Background: Fetal Growth Restriction (FGR) is a major cause of perinatal mortality and morbidity, often linked to placental insufficiency. Differentiating pathological growth restriction from constitutionally small-for-gestational-age (SGA) fetuses remains a clinical challenge. This study aims to evaluate the efficacy of a multi-modal screening approach combining biometry, Doppler velocimetry, and biochemical markers for the early diagnosis of FGR. Methods: A prospective cohort study involving 300 pregnant women was conducted. Participants underwent screening at 11-13 weeks and 20-24 weeks. The protocol included: assessment of maternal risk factors, Uterine Artery Pulsatility Index (UtA-PI) measurement, Cerebroplacental Ratio (CPR) calculation, and serum PlGF levels. Diagnosis accuracy was compared against postnatal birth weight centiles and neonatal outcomes. Results: Traditional biometry alone had a sensitivity of 45% for predicting FGR. The combined model (Biometry + UtA-PI + CPR + PlGF) significantly increased sensitivity to 88% ($p < 0.001$) with a false-positive rate of 8%. Low PlGF levels (<5th percentile) and abnormal CPR were strong independent predictors of adverse perinatal outcomes, even in fetuses with estimated weight >10th percentile. Conclusion: A combined screening strategy significantly improves the early detection of FGR compared to biometry alone. Integrating hemodynamic (Doppler) and metabolic (PlGF) markers allows for the identification of "at-risk" fetuses before growth lag becomes anatomically apparent.

Keywords: Fetal growth restriction, early diagnosis, Doppler ultrasonography, cerebroplacental ratio, PlGF, placental insufficiency.

HOMILA O‘SISHDAN ORQADA QOLISHINI ERTA TASHXISLASHNING ZAMONAVIY YONDASHUVLARI

Annotatsiya: Kirish: Homila o‘sishdan orqada qolishi (HOOQ) perinatal o‘lim va kasallanishning asosiy sabablaridan biri bo‘lib, ko‘pincha platsentar yetishmovchilik bilan bog‘liq. Patologik o‘sishdan orqada qolishni konstitutsional kichik (SGA) homiladan farqlash klinik muammo bo‘lib qolmoqda. Ushbu tadqiqot HOOQni erta tashxislash uchun biometriya, Doppler velosimetriya va biokimyoviy markerlarni birlashtirgan ko‘p modalli skrining yondashuvining samaradorligini baholashga qaratilgan. Usullar: 300 nafar homilador ayol ishtirokida prospektiv kohort tadqiqot o‘tkazildi. Ishtirokchilar 11-13 va 20-24 haftalik muddatlarda skriningdan o‘tkazildi. Protokolga quyidagilar kiritildi: onaning xavf omillarini baholash, Bachadon Arteriyasi Pulsatsiya Indeksi (UtA-PI), Serebroplatsentar Koeffitsiyent (CPR) va qon zardobidagi PlGF darajasi. Tashxis aniqligi tug‘ruqdan keyingi vazn sentillari va

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neonatal natijalar bilan solishtirildi. Natijalar: Faqat an'anaviy biometriya HOOQni bashorat qilishda 45% sezuvchanlikka ega bo'ldi. Kombinatsiyalashgan model (Biometriya + UtA-PI + CPR + PlGF) sezuvchanlikni 88% gacha sezilarli darajada oshirdi ($p < 0.001$), soxta musbat natijalar 8% ni tashkil etdi. PlGF ning past darajasi (<5-sentil) va g'ayritabiiy CPR, hatto vazni >10-sentil bo'lgan homilalarda ham salbiy perinatal oqibatlarning kuchli mustaqil prognoz omillari ekanligi aniqlandi. Xulosa: Kombinatsiyalashgan skrining strategiyasi faqat biometriyaga qaraganda HOOQni erta aniqlashni sezilarli darajada yaxshilaydi. Gemodinamik (Doppler) va metabolik (PlGF) markerlarni integratsiya qilish o'sishdan orqada qolish anatomik jihatdan namoyon bo'lishidan oldin "xavf ostidagi" homilalarni aniqlash imkonini beradi.
Kalit so'zlar: Homila o'sishdan orqada qolishi, erta tashxis, Doppler ultratovush, serebroplatsentar koeffitsiyent, PlGF, platsentar yetishmovchilik.

СОВРЕМЕННЫЕ ПОДХОДЫ К РАННЕЙ ДИАГНОСТИКЕ ЗАДЕРЖКИ РОСТА ПЛОДА

Аннотация: Введение: Задержка роста плода (ЗРП) является основной причиной перинатальной смертности и заболеваемости, часто связанной с плацентарной недостаточностью. Дифференциация патологической задержки роста от конституционально малого для гестационного возраста (МГВ) плода остается клинической проблемой. Данное исследование направлено на оценку эффективности мультимодального скрининга, сочетающего биометрию, допплерометрию и биохимические маркеры для ранней диагностики ЗРП. Методы: Было проведено проспективное когортное исследование с участием 300 беременных женщин. Участницы проходили скрининг на сроках 11-13 и 20-24 недели. Протокол включал: оценку материнских факторов риска, измерение пульсационного индекса маточных артерий (UtA-PI), цереброплацентарного отношения (CPR) и уровня PlGF в сыворотке. Точность диагностики сравнивалась с постнатальными центилями веса и неонатальными исходами. Результаты: Традиционная биометрия сама по себе имела чувствительность 45% для прогнозирования ЗРП. Комбинированная модель (Биометрия + UtA-PI + CPR + PlGF) значительно повысила чувствительность до 88% ($p < 0.001$) при уровне ложноположительных результатов 8%. Низкий уровень PlGF (<5-го центиля) и аномальный CPR были сильными независимыми предикторами неблагоприятных перинатальных исходов даже у плодов с предполагаемым весом >10-го центиля. Заключение: Стратегия комбинированного скрининга значительно улучшает раннее выявление ЗРП по сравнению с изолированной биометрией. Интеграция гемодинамических (Допплер) и метаболических (PlGF) маркеров позволяет выявлять плодов «группы риска» до того, как отставание в росте станет анатомически очевидным.
Ключевые слова: Задержка роста плода, ранняя диагностика, допплерография, цереброплацентарное отношение, PlGF, плацентарная недостаточность.

INTRODUCTION

Fetal Growth Restriction (FGR), previously termed intrauterine growth restriction (IUGR), represents one of the most complex, multifactorial, and critical challenges in modern obstetrics. It is clinically defined as the failure of the fetus to achieve its genetically determined growth

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potential, typically as a consequence of placental insufficiency. Globally, FGR affects approximately 5-10% of all pregnancies and is a leading contributor to perinatal mortality, accounting for up to 30-50% of stillbirths. The burden of this condition is not limited to the immediate neonatal period; according to the "Barker Hypothesis" (Developmental Origins of Health and Disease), growth-restricted fetuses undergo metabolic programming in utero to survive scarcity, placing them at significantly higher risk for long-term health issues, including cardiovascular disease, type 2 diabetes, and metabolic syndrome in adulthood.

In the context of Uzbekistan, and particularly in the Andijan region, the management of FGR takes on heightened importance due to specific demographic and epidemiological factors. The region is characterized by a high birth rate, young maternal age, and a significant prevalence of maternal comorbidities such as iron-deficiency anemia (affecting nearly 40% of pregnant women) and preeclampsia. These conditions act as potent risk factors for placental dysfunction, exacerbating the incidence of FGR.

A critical clinical dilemma lies in distinguishing true pathological FGR from "Small for Gestational Age" (SGA) fetuses. SGA fetuses are constitutionally small (often defined as weight <10th percentile) but physiologically healthy, with normal placental function and perinatal outcomes. In contrast, FGR fetuses are pathologically compromised, suffering from chronic hypoxia and malnutrition. The traditional diagnostic paradigm, which relies heavily on late third-trimester biometry (abdominal circumference and estimated fetal weight), is fraught with limitations. It often identifies the problem only when the fetus has already suffered significant growth lag or catabolism, leaving little room for preventative measures other than preterm delivery.

Moreover, relying solely on size misses a crucial subset of "Late-onset FGR" cases. In these scenarios, the fetus may be technically within the normal weight range (e.g., 15th percentile) but has failed to reach its personal potential (e.g., genetic target of 50th percentile) due to placental failure. These "occult" FGR cases are at particularly high risk of sudden intrauterine death because they are often classified as "low risk" by standard protocols and do not receive appropriate surveillance.

Modern obstetrics is shifting towards a proactive, functional approach known as the "Inverted Pyramid of Care." This involves prioritizing screening in the first and second trimesters and integrating multi-modal parameters. The hypothesis is that by combining detailed maternal history, advanced hemodynamic monitoring (Doppler velocimetry), and biochemical markers of placental function (such as PlGF), we can identify the "placenta at risk" weeks or months before the fetus becomes anatomically small. This study aims to evaluate such a contemporary algorithm in the local population to improve early prognosis, enabling timely interventions like aspirin prophylaxis and optimized delivery timing to improve perinatal outcomes.

LITERATURE REVIEW

The Limitations of Biometry and the "Iceberg Phenomenon" Ultrasound biometry has been the cornerstone of fetal surveillance for decades. Standard formulas utilize head circumference (HC), abdominal circumference (AC), and femur length (FL) to calculate Estimated Fetal Weight (EFW). However, reliance on EFW <10th percentile as the sole diagnostic criterion is increasingly questioned. *Sovio et al. (2015)* in the landmark Pregnancy Outcome Prediction (POP) study demonstrated that universal third-trimester ultrasound for EFW <10th percentile

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misses more than 50% of fetuses that are at risk of stillbirth or neonatal acidosis. The study highlighted that AC is a late marker of malnutrition; the fetal liver (which determines AC size due to glycogen storage) depletes its stores and shrinks only after prolonged deprivation. Consequently, biometry alone detects the "tip of the iceberg," leaving many functionally compromised fetuses undiagnosed until fetal distress occurs during labor.

Pathophysiological Mechanisms: Early vs. Late FGR The pathophysiology of FGR is primarily rooted in defective placentation, but the mechanisms differ by gestational age.

Early-onset FGR (<32 weeks): The mechanism typically involves severe impairment of trophoblast invasion into the maternal spiral arteries in the first trimester. This leads to high-resistance maternal blood flow, placental ischemia, and severe fetal hypoxia. It is often associated with preeclampsia and is easier to diagnose (small fetus + abnormal umbilical Doppler) but harder to manage due to prematurity.

Late-onset FGR (≥32 weeks): The defect is often subtler—a mismatch between the exponentially increasing metabolic demands of the growing fetus and the limited transport capacity of a senescent or slightly damaged placenta. In these cases, the umbilical artery resistance may remain normal, but the fetus suffers from chronic hypoxemia. *Gordijn et al. (2016)*, in the Delphi consensus, emphasized that FGR should be defined not just by size, but by functional evidence of starvation and hypoxia (arrested growth trajectory).

The Hemodynamic Revolution: Doppler Ultrasonography Doppler velocimetry allows for the non-invasive assessment of the fetoplacental circulation, serving as a functional "stress test."

Uterine Artery (UtA): High resistance or "notching" in the UtA waveforms at 11-13 weeks or 20-24 weeks is a strong predictor of early-onset PE and FGR, reflecting failed spiral artery remodeling. It assesses the *maternal* side of the placenta.

Umbilical Artery (UA): The UA reflects *placental* vascular resistance. While absent or reversed end-diastolic flow is a hallmark of severe, early FGR, UA Doppler is frequently normal in late-onset FGR because the placental damage is not extensive enough to alter global resistance, yet sufficient to cause hypoxia.

Middle Cerebral Artery (MCA) & Cerebroplacental Ratio (CPR): The MCA is critical for assessing fetal adaptation. When the placenta fails, the fetus initiates a "brain-sparing effect"—vasodilation of cerebral vessels to preserve oxygen for the brain while constricting systemic vessels (gut, kidneys). The CPR, calculated as MCA-PI divided by UA-PI, amplifies these subtle changes. A low CPR (<5th percentile) is independently associated with urgent cesarean section for fetal distress and adverse neurodevelopmental outcomes, even in fetuses with normal EFW.

Biochemical Markers - The Role of Angiogenic Factors The balance between angiogenic factors (like Placental Growth Factor - PlGF) and anti-angiogenic factors (like Soluble Fms-like Tyrosine Kinase-1 - sFlt-1) dictates placental health. In normal pregnancy, PlGF levels rise significantly until 30 weeks to support villous growth. In placental insufficiency, PlGF levels are markedly low. The *DELPHI study* and subsequent validation trials have confirmed that low PlGF is a potent predictor of FGR, capable of distinguishing constitutional SGA (normal PlGF) from pathological FGR (low PlGF). The sFlt-1/PlGF ratio is now clinically used in Europe to predict the short-term absence of preeclampsia/FGR, but its use in Central Asia remains limited. Integrating PlGF into first-trimester screening algorithms allows for the stratification of women into high-risk groups who may benefit from low-dose aspirin prophylaxis.

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Combined Screening Models Current international guidelines (ISUOG, FIGO) advocate for a "Combined Screening Test." *Poon et al. (2016)* demonstrated that an algorithm combining maternal factors (MAP), UtA Doppler, and biochemical markers can predict >90% of early-onset FGR cases. However, the implementation of such complex models in low-to-middle-income settings requires validation. This study seeks to bridge the gap between these advanced theoretical models and clinical practice in the Andijan region.

MATERIALS AND METHODS

Study Design A prospective cohort study was conducted at the Andijan Regional Perinatal Center and University Clinic over an 18-month period (2023-2024). Participants 300 pregnant women with singleton pregnancies were recruited at 11-13 weeks.

Exclusion Criteria: Multiple pregnancies, major congenital anomalies, chromosomal defects. Screening Algorithm Participants underwent a two-stage screening process: Stage 1 (11-13 weeks): 1) Maternal History (Age, BMI, Parity, Previous FGR/PE). 2) Mean Arterial Pressure (MAP). 3) Uterine Artery Doppler (UtA-PI). 4) Serum PAPP-A and PlGF. Stage 2 (20-24 weeks): 1) Detailed anomaly scan + Biometry (EFW). 2) Repeat UtA-PI. 3) Cerebroplacental Ratio (CPR) assessment.

Early FGR - diagnosed <32 weeks based on Delphi consensus (AC/EFW <3rd percentile OR absent end-diastolic flow in UA).

Late FGR - diagnosed ≥32 weeks (AC/EFW <3rd percentile OR EFW <10th percentile with abnormal CPR/UtA-PI).

Statistical Analysis Diagnostic performance (Sensitivity, Specificity, Positive Predictive Value) was calculated for different screening models.

RESULTS

Incidence Of the 300 pregnancies, 32 (10.6%) were diagnosed with FGR postnatally (birth weight <10th percentile with signs of malnutrition). Diagnostic Accuracy of Screening Models We compared three diagnostic approaches:

Table 1: Prediction of FGR (Detection Rate at 10% False Positive Rate)

Screening Method	Detection Rate (%)
Model A: Routine Biometry only (EFW <10th)	45%
Model B: Biometry + Uterine Artery Doppler	68%
Model C: Biometry + Doppler (UtA + CPR) + PlGF	88%

Model C (Combined) showed the highest sensitivity. Notably, 20% of fetuses with FGR had an estimated weight *above* the 10th percentile but showed signs of "brain sparing" (low CPR), which would have been missed by biometry alone.

The Role of PlGF Women with PlGF levels <5th percentile at 20-24 weeks had a 9-fold increased risk of delivering an FGR baby (OR 9.2; 95% CI 4.5-18.1). Low PlGF was particularly effective in predicting early-onset severe FGR requiring delivery before 34 weeks.

Perinatal Outcomes Fetuses identified as "High Risk" by the combined model (Model C) but "Normal" by biometry alone had significantly worse outcomes (NICU admission, acidosis) than true low-risk fetuses, confirming that the combined model detects true pathology.

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DISCUSSION

This study highlights the paradigm shift from "measuring size" to "assessing function" in FGR diagnosis. Biometry is Insufficient: Relying solely on fetal size (abdominal circumference) is inadequate because fetal growth deceleration often precedes the drop below the 10th percentile. By the time a fetus is anatomically small, significant hypoxic damage may have occurred.

The Power of Doppler: The inclusion of the Cerebroplacental Ratio (CPR) was a game-changer in our cohort. A low CPR indicates that the fetus is redistributing blood flow to the brain, a classic sign of hypoxia. This marker allows us to identify "growth-restricted" fetuses who are not yet "small" (e.g., a fetus genetically destined to be 3.5kg dropping to 2.8kg is technically normal size but functionally restricted).

Biochemical Adjuncts: PlGF serves as a "placental fuel gauge." Low levels indicate a failing placenta long before Doppler changes occur. In the Andijan region, introducing PlGF testing could significantly refine risk stratification, allowing resources to be focused on the highest-risk pregnancies.

CONCLUSION

Early diagnosis of FGR requires a multi-parametric approach that looks beyond simple weight estimation.

Integrating maternal history, Doppler (UtA, CPR), and biomarkers (PlGF) doubles the detection rate of FGR compared to routine ultrasound alone.

Doppler markers like CPR are critical for identifying late-onset FGR where fetal size may be normal.

Early identification allows for closer surveillance and optimal timing of delivery to prevent stillbirth.

Routine anomaly scans (20-24 weeks) should include Uterine Artery Doppler screening.

In suspected cases of growth slowing (even if weight is >10th percentile), CPR measurement should be mandatory.

PlGF testing should be introduced for high-risk groups (hypertensive, history of FGR).

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