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ORIGINAL RESEARCH

Predictive Value of Proteinuria at the Time of IUGR Diagnosis for the Development of Preeclampsia or Gestational Hypertension

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ABSTRACT

Intrauterine growth restriction (IUGR) is a major cause of perinatal morbidity and mortality, primarily resulting from uteroplacental insufficiency and maternal vascular dysfunction. Although proteinuria is traditionally a diagnostic criterion for preeclampsia, it may also have predictive value in normotensive pregnancies complicated by IUGR. This study aimed to evaluate whether proteinuria detected at the time of IUGR diagnosis in normotensive pregnancies predicts subsequent development of preeclampsia or gestational hypertension (PE/GHT). This retrospective cohort study included 180 women diagnosed with IUGR between 24–32 weeks of gestation at a tertiary perinatal center. Women with chronic hypertension, renal disease, diabetes, or multiple gestation were excluded. Proteinuria was assessed by either 24-hour urine collection (n = 106) or spot urine protein/creatinine (Pr/Cr) ratio (n = 74). Proteinuria was defined as ≥300 mg/day or Pr/Cr ≥0.30. The primary outcome was development of PE/GHT, analyzed using receiver operating characteristic (ROC) curves.

In the 24-hour urine group, 68.8% of proteinuria-positive women and 16.2% without proteinuria developed PE/GHT ($p < 0.001$; AUC = 0.82, optimal cut-off 319.6 mg/day). In the spot Pr/Cr group, 75.0% of proteinuria-positive and 17.6% of proteinuria-negative women developed PE/GHT ($p < 0.001$; AUC = 0.89, cut-off 0.30).

Proteinuria-positive women were approximately 4–5 times more likely to develop PE/GHT. Proteinuria detected at IUGR diagnosis—whether measured by 24-hour urine or spot Pr/Cr ratio—is a strong predictor of later hypertensive disorders. The spot Pr/Cr ratio provides comparable predictive accuracy and represents a practical, rapid screening method for early risk assessment in normotensive IUGR pregnancies.

Keywords: Intrauterine growth restriction (IUGR). Proteinuria. Preeclampsia. Gestational hypertension. Protein/creatinine ratio. Prediction. Placental insufficiency.

İUGR Tanısı Anında Saptanan Proteinürinin Preeklampsi veya Gestasyonel Hipertansiyon Gelişimini Öngörmedeki Değeri

İUGR Olgularında Preeklampsinin Erken Belirteci Olarak Proteinüri

ÖZET

İntrauterin büyüme kısıtlılığı (İUGR), esas olarak uteroplasental yetersizlik ve maternal vasküler disfonksiyon sonucu gelişen, perinatal morbidite ve mortalitenin önemli nedenlerinden biridir. Proteinüri klasik olarak preeklampsi tanı kriterlerinden biri olarak kabul edilse de, İUGR ile komplike olmuş normotansif gebeliklerde de öngörü değeri taşıyabilir. Bu çalışmanın amacı, İUGR tanısı anında saptanan proteinürinin sonraki dönemde preeklampsi veya gestasyonel hipertansiyon (PE/GHT) gelişimini öngörüp öngörmediğini değerlendirmektir.

Bu retrospektif kohort çalışmaya, 24–32. gebelik haftaları arasında İUGR tanısı alan 180 kadın dahil edilmiştir. Kronik hipertansiyon, böbrek hastalığı, diyabet veya çoğul gebeliği olan olgular dışlanmıştır. Proteinüri, 24 saatlik idrar toplama (n = 106) veya spot idrar protein/kreatinin (Pr/Cr) oranı (n = 74) ile değerlendirilmiş; ≥300 mg/gün veya Pr/Cr ≥0,30 proteinüri olarak kabul edilmiştir. Birincil sonuç değişkeni, preeklampsi veya gestasyonel hipertansiyon gelişimi olup, alıcı işletim karakteristiği (ROC) eğrisi analizi ile öngörü gücü değerlendirilmiştir.

Proteinürisi olan olguların %68,8'i (24 saatlik test) ve %75,0'ı (spot test) PE/GHT geliştirmiştir; buna karşın proteinürisi olmayanlarda bu oran sırasıyla %16,2 ve %17,6'dır (her ikisi için $p < 0,001$). AUC değerleri sırasıyla 0,82 ve 0,89 bulunmuştur.

Proteinürisi pozitif kadınlarda PE/GHT gelişme olasılığı yaklaşık 4–5 kat daha yüksektir. İUGR tanısı anında saptanan proteinüri, sonraki hipertansif hastalıklar için güçlü bir öngördürücüdür. Spot Pr/Cr oranı, 24 saatlik testle benzer doğruluk göstermiş olup, normotansif İUGR gebeliklerinde erken risk değerlendirmesi için pratik ve hızlı bir yöntemdir.

Anahtar Kelimeler: İntrauterin büyüme kısıtlılığı (İUGR). Proteinüri. Preeklampsi. Gestasyonel hipertansiyon. Protein/kreatinin oranı. Öngörü. Plasental yetersizlik.

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Intrauterine growth restriction (IUGR) affects approximately 5–10% of all pregnancies and remains one of the leading causes of perinatal morbidity and mortality worldwide[1,2]. IUGR is defined as the failure of the fetus to achieve its genetically determined growth potential and is most often a clinical manifestation of placental insufficiency. The underlying pathophysiology involves impaired uteroplacental perfusion and abnormal maternal vascular remodeling, which are frequently associated with maternal disorders such as chronic hypertension, preeclampsia, and systemic inflammation[1-3]. Beyond its immediate implications for perinatal outcome, IUGR also reflects an altered maternal-fetal environment characterized by endothelial dysfunction and maladaptive placental angiogenesis, both of which play pivotal roles in the pathogenesis of hypertensive disorders of pregnancy[3,4].

Preeclampsia and gestational hypertension (GHT) represent two major hypertensive disorders that typically develop during the second half of pregnancy. These conditions are responsible for substantial maternal and fetal complications, including preterm birth, placental abruption, fetal growth restriction, and perinatal death[5,6]. Early identification of women at increased risk for these disorders is therefore of paramount importance to improve outcomes through timely surveillance and intervention. Despite numerous proposed biomarkers—ranging from angiogenic factors such as placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) to biochemical markers reflecting oxidative stress and endothelial injury—routine clinical prediction remains challenging, particularly in normotensive women already diagnosed with IUGR[7,8].

Proteinuria has long been regarded as one of the diagnostic hallmarks of preeclampsia. Traditionally, it was considered a binary diagnostic threshold (≥300 mg/day in a 24-hour urine sample or a spot urine protein/creatinine ratio ≥0.30)[5,6]. However, growing evidence suggests that proteinuria may also carry prognostic value, reflecting the extent of systemic endothelial dysfunction and glomerular injury preceding overt hypertension[9,10]. In this context, early detection of proteinuria—even in normotensive pregnancies—could serve as a subclinical indicator of vascular pathology and predict subsequent development of preeclampsia or GHT.

Several studies have explored the association between early or isolated proteinuria and adverse maternal outcomes, yet few have focused on women with IUGR, a population already characterized by impaired placental perfusion[10,11]. Because IUGR and preeclampsia share overlapping pathophysiological mechanisms—particularly involving abnormal spiral artery remodeling, increased placental resistance, and maternal systemic inflammation—presence of proteinuria at the time of IUGR diagnosis may reflect the early stages of the preeclampsia spectrum. Moreover, differentiating between IUGR as a placental phenotype and preeclampsia as a maternal endothelial disorder remains a clinical challenge, making simple biochemical predictors valuable in identifying patients at higher risk for progression.

From a practical standpoint, the measurement of urinary protein can be performed either via a 24-hour urine collection, considered the gold standard, or by a spot urine protein-to-creatinine (Pr/Cr) ratio, which provides a rapid and convenient alternative[12]. While both methods are widely used in clinical practice, their comparative predictive performance for future hypertensive complications in normotensive IUGR pregnancies has not been systematically evaluated. Understanding the predictive accuracy of these measurements could aid in the development of risk-based surveillance protocols, allowing for closer monitoring and earlier intervention in high-risk patients.

Therefore, the present study aimed to evaluate the predictive value of proteinuria detected at the time of IUGR diagnosis—assessed either by 24-hour urine protein excretion or by spot urine protein/creatinine ratio—for the subsequent development of preeclampsia or gestational hypertension. We hypothesized that the presence of proteinuria in normotensive women with IUGR reflects underlying placental and endothelial dysfunction and may serve as an early marker of impending hypertensive disease later in pregnancy. This study provides new insights into the prognostic role of proteinuria in the continuum between placental insufficiency and maternal hypertensive disorders.

Material and Method

Study Design and Setting

This retrospective cohort study was conducted at a tertiary referral perinatology center between January 2020 and December 2024. The study protocol was reviewed and approved by the institutional ethics committee and performed in accordance with the principles of the Declaration of Helsinki.

Study Population

Eligible participants were pregnant women diagnosed with intrauterine growth restriction (IUGR) between 24 and 32 weeks of gestation. The diagnosis of IUGR was based on ultrasonographic findings of an estimated fetal weight (EFW) below the 10th percentile for gestational age, confirmed by serial biometric measurements and Doppler velocimetry consistent with placental insufficiency (e.g., increased

umbilical artery pulsatility index or absent/reversed end-diastolic flow).

To minimize confounding factors, only normotensive women at the time of IUGR diagnosis were included. Blood pressure measurements were taken in a seated position using an automated sphygmomanometer, and the average of two consecutive readings was recorded.

Inclusion Criteria

- Singleton pregnancy
- Gestational age between 24 and 32 weeks at IUGR diagnosis
- Absence of hypertension or preeclampsia at diagnosis
- Availability of either 24-hour urine protein measurement or spot urine protein/creatinine (Pr/Cr) ratio at the time of diagnosis
- Follow-up until delivery with complete outcome data

Exclusion Criteria

- Preexisting chronic hypertension
- Known renal disease or urinary tract infection
- Pregestational or gestational diabetes mellitus
- Multiple gestations
- Autoimmune or systemic inflammatory disease
- Missing or incomplete medical records

Information regarding low-dose aspirin prophylaxis was not uniformly available in the medical records. However, no participant was receiving antihypertensive therapy at the time of IUGR diagnosis.

Assessment of Proteinuria

At the time of IUGR diagnosis, all participants underwent routine laboratory evaluation including urine analysis.

24-hour urine collection: Samples were considered valid if total volume exceeded 1000 mL and creatinine excretion fell within the expected physiologic range. Proteinuria was defined as ≥300 mg/day.

Spot urine protein/creatinine ratio (Pr/Cr): Measured from a random midstream sample, with proteinuria defined as Pr/Cr ≥0.30.

Each patient had only one test performed (either 24-hour collection or spot Pr/Cr ratio), selected based on clinical availability and physician preference at the time of presentation.

Definition of Outcomes

The primary outcome was the development of preeclampsia or gestational hypertension (GHT) later in pregnancy.

Preeclampsia was defined according to the criteria of the American College of Obstetricians and Gynecologists (ACOG) as new-onset hypertension (systolic ≥140 mmHg and/or diastolic ≥90 mmHg on two occasions at least 4 hours apart) after 20 weeks of gestation accompanied by proteinuria (≥300 mg/day or Pr/Cr ≥0.30) or evidence of systemic involvement (thrombocytopenia, elevated liver enzymes, renal insufficiency, pulmonary edema, or new-onset cerebral or visual symptoms)[5].

Gestational hypertension was defined as new-onset hypertension after 20 weeks of gestation in the absence of proteinuria or systemic organ involvement[5].

The diagnosis and clinical course of hypertensive disorders were confirmed through follow-up visits and electronic medical records up to delivery.

Statistical Analysis

All analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA).

Continuous variables were presented as mean ± standard deviation (SD), and categorical variables as numbers and percentages. Student's t-test or Mann–Whitney U test was used for comparison of continuous variables, while chi-square test (χ^2) or Fisher's exact test was used for categorical data.

Receiver operating characteristic (ROC) curve analysis was conducted to determine the predictive performance of both 24-hour urine protein and spot Pr/Cr ratio for preeclampsia/GHT development. The area under the curve (AUC), optimal cut-off values, sensitivity, and specificity were calculated. A p-value of <0.05 was considered statistically significant.

Sample Size and Grouping

- A total of 180 women met the inclusion criteria. Among them,
- 106 underwent 24-hour urine testing, and
- 74 underwent spot urine Pr/Cr ratio testing.
- No patient was included in both groups.

Results

Study Population

A total of 180 women with a diagnosis of IUGR between 24 and 32 weeks of gestation were included in the final analysis. The mean maternal age was 31.1 ± 5.4 years, the mean gravida 2.3 ± 1.2, parity 1.0 ± 1.1, abortion history 0.3 ± 0.7, and body mass index (BMI) 26.4 ± 4.6 kg/m².

Among these, 106 (58.9%) underwent 24-hour urine protein measurement, while 74 (41.1%) underwent spot urine protein/creatinine (Pr/Cr) ratio testing.

None of the participants had preeclampsia or hypertension at the time of inclusion. Baseline demographic and obstetric characteristics (age, parity, BMI, and gestational age at diagnosis) were comparable between the 24-hour and spot urine test groups, with no statistically significant differences observed ($p > 0.05$ for all).

Maternal Demographic and Clinical Characteristics

Baseline demographic and obstetric characteristics were comparable between women who subsequently developed preeclampsia or gestational hypertension (PE/GHT group) and those who remained normotensive throughout pregnancy (control group).

As shown in Table I, no significant differences were observed in maternal age, gravida, parity, abortion history, or BMI between the two groups.

Table I. Maternal demographic and clinical characteristics according to the development of preeclampsia/GHT

Parameter	PE/GHT (mean ± SD)	No PE/GHT (mean ± SD)	*p*-value
Age (years)	31.56 ± 5.19	30.85 ± 5.53	0.364
Gravida	2.39 ± 1.25	2.32 ± 1.24	0.707
Parity	1.06 ± 1.10	1.04 ± 1.13	0.893
Abortus	0.33 ± 0.86	0.28 ± 0.68	0.692
BMI (kg/m²)	26.47 ± 4.73	26.30 ± 4.52	0.794

No baseline demographic factor was significantly associated with later development of hypertensive disorders ($p > 0.05$ for all comparisons).

24-Hour Urine Protein Test Group

Among the 106 women who underwent 24-hour urine collection:

- 32 (30.2%) had proteinuria (≥ 300 mg/day).
- During follow-up, 22 of the 32 proteinuria-positive women (68.8%) developed preeclampsia or GHT, compared with 12 of the 74 proteinuria-negative women (16.2%).
- This difference was statistically significant ($p < 0.001$), indicating a strong association between proteinuria and subsequent hypertensive disorders.

ROC curve analysis for the 24-hour urine test revealed an area under the curve (AUC) of 0.82, demonstrating good discriminative performance in predicting later PE/GHT. The optimal cut-off value was 319.6 mg/day, close to the conventional diagnostic threshold of 300 mg/day, yielding high sensitivity and specificity (Figure 1).

Spot Urine Protein/Creatinine Ratio Group

Among the 74 women evaluated by spot Pr/Cr ratio:

- 40 (54.1%) were proteinuria-positive (Pr/Cr ≥ 0.30),
- 34 (45.9%) were proteinuria-negative (Pr/Cr < 0.30).
- During follow-up, 30 of 40 proteinuria-positive women (75.0%) developed preeclampsia or GHT, compared with 6 of 34 proteinuria-negative women (17.6%).
- The difference was highly significant ($p < 0.001$).

ROC analysis demonstrated an AUC of 0.89, indicating excellent predictive accuracy for PE/GHT development. The optimal cut-off value (0.30) corresponded exactly to the widely accepted clinical threshold, supporting its validity in this population (Figure 1).

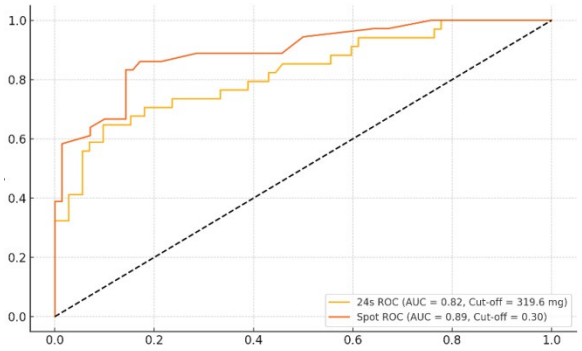

Figure 1.
ROC Curves According to 24-Hour and Spot Urine Tests

Comparative Predictive Performance

When the two testing modalities were compared, the spot Pr/Cr ratio yielded a slightly higher AUC than the 24-hour urine test (0.89 vs 0.82), suggesting superior predictive capacity.

However, both tests demonstrated strong associations between proteinuria at the time of IUGR diagnosis and subsequent hypertensive disease.

Women with proteinuria were approximately 4–5 times more likely to develop preeclampsia or gestational hypertension later in pregnancy than those without proteinuria.

Discussion and Conclusion

This study demonstrated that the presence of proteinuria at the time of IUGR diagnosis is a strong and independent predictor of subsequent development of preeclampsia or gestational hypertension (PE/GHT) in previously normotensive women. Both 24-hour urine protein excretion and spot urine protein/creatinine (Pr/Cr) ratio showed significant predictive value, with high areas under the ROC curve (AUC = 0.82 and 0.89, respectively). These findings

suggest that subclinical proteinuria in IUGR pregnancies may reflect early endothelial dysfunction and evolving placental disease, preceding the clinical onset of hypertensive disorders.

Proteinuria as a Marker of Vascular Dysfunction

Proteinuria has long been used as a diagnostic criterion for preeclampsia; however, its pathophysiologic significance extends beyond diagnosis. Protein leakage into urine reflects glomerular endotheliosis, a manifestation of systemic endothelial injury characteristic of preeclampsia[5,13]. In pregnancies complicated by IUGR, similar vascular and placental abnormalities,such as inadequate trophoblastic invasion and impaired spiral artery remodeling—contribute to uteroplacental insufficiency. Thus, proteinuria identified at the time of IUGR diagnosis may indicate early renal and systemic endothelial compromise, positioning it as a potential early marker in the preeclampsia continuum.

Consistent with this concept, prior studies have reported that increased urinary protein levels, even below the diagnostic threshold, are associated with later hypertensive complications and adverse perinatal outcomes[14,15]. The present results extend this observation to a specific high-risk subgroup—normotensive women with IUGR, highlighting that even modest proteinuria should not be dismissed as benign in this context.

Comparison Between Testing Modalities

The comparative analysis between 24-hour urine collection and spot Pr/Cr ratio revealed that both methods are reliable in predicting hypertensive disorders. The spot test, however, exhibited a slightly higher AUC (0.89 vs. 0.82), suggesting superior or at least equivalent diagnostic accuracy with greater clinical convenience. These results align with those of earlier validation studies, which established that the spot Pr/Cr ratio correlates strongly with 24-hour protein excretion and can effectively substitute for it in both diagnostic and monitoring settings[16-19].

Given its simplicity, noninvasiveness, and faster turnaround time, the spot test may represent a more practical tool for early risk stratification in outpatient and resource-limited environments.

Pathophysiological Link Between IUGR and Preeclampsia

IUGR and preeclampsia share a common pathogenic pathway involving defective placentation and maternal vascular maladaptation. Abnormal remodeling of the spiral arteries results in reduced uteroplacental perfusion, leading to placental ischemia and the release of antiangiogenic and inflammatory mediators such as sFlt-1 and endoglin. These factors contribute to widespread maternal endothelial dysfunction, hypertension, and renal involvement[20,21].

The identification of proteinuria in normotensive IUGR cases may therefore signify an early stage in this cascade, before the clinical manifestation of hypertension. The predictive relationship demonstrated in this study supports the view that proteinuria and IUGR may represent different phenotypic expressions of the same placental pathology, differing only in timing and systemic impact.

Clinical Implications

From a clinical standpoint, these findings suggest that proteinuria testing at the time of IUGR diagnosis could provide valuable prognostic information. Women who present with IUGR and concomitant proteinuria—even in the absence of hypertension—should be considered at increased risk for developing preeclampsia or gestational hypertension. Such patients may benefit from intensified monitoring, including more frequent blood pressure assessments, laboratory evaluations (renal and liver function, platelet count), and fetal surveillance with Doppler studies.

Moreover, early identification of high-risk women could guide timely referral to tertiary centers, facilitate counseling regarding potential complications, and enable preventive strategies such as low-dose aspirin continuation, optimization of delivery timing, and neonatal preparedness.

The comparable predictive performance of the spot urine Pr/Cr ratio also supports its incorporation into routine clinical protocols, particularly in settings where 24-hour collection is impractical or poorly tolerated by patients. Its use could enhance clinical efficiency without compromising accuracy.

In clinical practice, proteinuria assessment may be repeated periodically in IUGR cases—particularly every 2–3 weeks or upon any change in maternal symptoms—to monitor evolving risk. Incorporating this step into standard IUGR follow-up protocols could facilitate earlier detection of hypertensive disorders. These findings may support integrating spot urine Pr/Cr ratio testing into routine evaluation at the time of IUGR diagnosis as a practical screening tool.

Comparison with the Literature

Previous studies have primarily focused on predicting preeclampsia based on angiogenic markers (PlGF, sFlt-1/PlGF ratio) or uterine artery Doppler indices[22,23]. However, these tests are not universally available and may be cost-prohibitive in low-resource settings. In contrast, urinary protein assessment remains inexpensive, widely accessible, and easily repeatable.

Our findings corroborate the results of studies emphasizing that even modest elevations in protein excretion can provide meaningful insight into maternal vascular status[24,25]. Notably, few prior works have specifically evaluated proteinuria in IUGR pregnancies as a predictive rather than diagnostic biomarker—making the current study a novel contribution to the literature[26-30]. Although angiogenic biomarkers such as sFlt-1 and PlGF were not available in this dataset, their inclusion in future predictive models could further improve the identification of women at risk for hypertensive complications.

Strengths and Limitations

The major strengths of this study include its relatively large, well-defined IUGR cohort and the dual assessment of proteinuria by two standardized methods. The inclusion of only normotensive women at baseline allows for clearer interpretation of proteinuria as a predictive rather than diagnostic variable.

However, certain limitations should be acknowledged. The retrospective design introduces potential selection and measurement bias. The study did not control for all confounding variables such as maternal renal function markers (e.g., serum creatinine, uric acid) or angiogenic factor levels, which could have enhanced mechanistic understanding. Another limitation was the lack of complete information on low-dose aspirin use at the time of IUGR diagnosis, which could have influenced the subsequent development of hypertensive disorders. In addition, the absence of a longitudinal follow-up on postpartum outcomes limits the extrapolation of results to long-term maternal cardiovascular risk. Prospective multicenter studies integrating biochemical and Doppler parameters are warranted to validate these findings and refine prediction algorithms.

In summary, this study provides evidence that proteinuria detected at the time of IUGR diagnosis, whether by 24-hour urine protein measurement or spot Pr/Cr ratio, is a significant predictor of subsequent preeclampsia or gestational hypertension. The strong association between early proteinuria and later hypertensive disease underscores the shared pathophysiologic continuum between placental dysfunction and maternal vascular injury.

Given its accessibility and predictive power, routine assessment of proteinuria in IUGR pregnancies could serve as a simple yet valuable tool for early risk stratification and individualized antenatal surveillance.

Researcher Contribution Statement:
Idea and design: S.E.Y, N.N; Data collection and processing: S.E.Y, N.N; Analysis and interpretation of data: S.E.Y, N.N; Writing of significant parts of the article: S.E.Y; Review and editing: S.E.Y.

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