

Clinical Significance of Isolated Gestational Proteinuria: A Prospective Analysis of Maternal and Neonatal Outcomes

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ABSTRACT Objective: This study aimed to investigate maternal and fetal outcomes in patients with isolated gestational proteinuria (IGP) and identified risk factors for developing preeclampsia (PE). **Material and Methods:** This prospective case-control study was conducted between April 2018 and January 2020 at a tertiary center. In this research, total protein levels were measured in 24-hour urine samples from second-trimester normotensive patients who exhibited proteinuria of ≥ 1 on a dipstick test. Three groups were defined at the outset: Group 1 (IGP group, n=41): Pregnant women with proteinuria ≥ 300 mg/24-hour without hypertension. Group 2 (IGP onset PE group, n=10): Pregnant women with proteinuria ≥ 300 mg/24-hour who later developed hypertension. Group 3 (Control group, n=84): Pregnant women without proteinuria (< 300 mg/24-hour) and hypertension during antenatal follow-up formed the control group. Maternal and neonatal outcomes of each group were compared. **Results:** Maternal and neonatal outcomes, including gestational age at delivery, preterm birth, delivery mode, and neonatal intensive care admissions, were similar between the IGP and control groups. The progression rate of IGP to PE was 19.6% (10/51). The overall prevalence of PE was 2.04% (195/9,520). Based on these findings, IGP was associated with a 12-fold increased risk of developing PE (OR 11.6, 95% CI 5.7-23.6; $p < 0.001$). Additionally, younger maternal age and previous PE history were found as risk factors in the progression of IGP to PE. **Conclusion:** Unless hypertension develops in IGP, there is no difference between maternal and neonatal outcomes in pregnant women with IGP and healthy pregnant women.

Keywords: Isolated proteinuria; gestational proteinuria; proteinuria; pregnancy; preeclampsia

Preeclampsia (PE) affects 2%-8% of pregnancies and is one of the leading causes of maternal, fetal, and neonatal mortality.¹⁻⁶ Traditionally, one of the primary diagnostic criteria for PE was the presence of proteinuria, defined as excessive protein excretion in the urine.⁷ However, in a pivotal shift in 2013, the American College of Obstetricians and Gynecologists (ACOG) introduced an alternative diagnostic criterion for PE that did not necessarily require proteinuria.⁸ This change marked a significant departure from the classic diagnostic framework for PE,

in which proteinuria had been a central element. Additionally, the updated criteria for severe PE no longer include massive proteinuria (previously defined as ≥ 5 grams in a 24-hour urine sample) as a determinant of severity. Although studies suggest that there is no strong correlation between the amount of proteinuria and the severity of PE or pregnancy outcomes, most women diagnosed with PE still exhibit proteinuria.⁸⁻¹⁰ Consequently, some researchers have proposed that proteinuria may serve as an “early sign” of PE.^{1,11,12}

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Isolated gestational proteinuria (IGP) refers to transient proteinuria of ≥ 300 mg/24-hour that appears after the 20th week of pregnancy and resolves within 12 weeks postpartum without the development of hypertension.¹² According to the current diagnostic criteria, IGP is retrospectively diagnosed in women who present with proteinuria during pregnancy but do not subsequently develop hypertension.^{12,13} However, the classification and understanding of IGP remains controversial in the medical community. Some debate whether IGP detected in early pregnancy is a variant of PE or a distinct, subclinical kidney disease specific to pregnancy.^{1,2} Moreover, there is limited data on the maternal and neonatal outcomes of pregnancies complicated by IGP.^{12,14}

Almost all studies on pregnant women with IGP are retrospective in nature. Our prospective study aims to address these knowledge gaps by following pregnant women diagnosed with IGP throughout pregnancy until delivery. Our primary objective is to establish the prevalence of PE in pregnant women with IGP and explore the associated risks. We also aim to perform a comparative analysis of maternal and neonatal outcomes in pregnant women with IGP who do not develop PE compared with healthy pregnant women.

MATERIAL AND METHODS

STUDY DESIGN

This prospective case-control study was conducted at the Department of Obstetrics and Gynecology, University of Health Sciences Tepecik Training and Research Hospital, from April 2018 to January 2020. This study was conducted following the Helsinki Declaration Ethical Standards. The ethics committee approval for this study was obtained from the University of Health Sciences Tepecik Training and Research Hospital Local Ethics Committee (date: March 21, 2018, no: 2018/2-15). All participants were informed and informed voluntary consent was obtained.

STUDY SETTING

Our institution is the largest referral center in the western region of Türkiye, managing a substantial

population of high-risk pregnancies. The neonatal unit is a level III facility, indicating advanced capabilities for managing complex neonatal conditions.

PATIENT EVALUATION

All pregnant women received comprehensive antenatal care, including 10-12 visits prior to delivery. During routine first-trimester screening, all participants underwent dipstick testing of random midstream urine samples and were found to have no proteinuria. Subsequent screening for proteinuria was conducted at or after 20 weeks of gestation, along with measurements of blood pressure and body weight. Proteinuria levels were measured using a dipstick test on random midstream urine samples. Patients with dipstick results showing proteinuria below +1 were excluded from the study, except for those who were included in the control group. Additional exclusion criteria included the use aspirin (acetylsalicylic acid), assisted reproductive techniques, hypertensive disorders, pregestational or gestational diabetes mellitus (GDM), thyroid disorders, renal diseases, urinary infection, multiple pregnancy, intrauterine fetal death, fetal anomaly, systemic diseases (e.g., autoimmune or collagen vascular diseases), and those who opted to withdraw from the study (e.g., delivered in another facility and declined sharing their records) (Figure 1).

We measured total protein output in 24-hour urine samples of normotensive pregnant women (systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg) with +1 proteinuria and above. Three groups were defined at the outset: Group 1 (IGP group): Pregnant women with proteinuria ≥ 300 mg/24-hour without hypertension. Group 2 (IGP onset PE group): Pregnant women with proteinuria ≥ 300 mg/24-hour who later developed hypertension. Group 3 (Control group): Pregnant women without proteinuria (< 300 mg/24-hour) and hypertension during antenatal follow-up formed the control group. We measured blood pressure and body weight of all patients in the study population at the visit. At the end of the clinical follow-up, we decided which patient would be recruited to which group.

For potential PE cases, we conducted weekly follow-up sessions for patients with proteinuria ex-

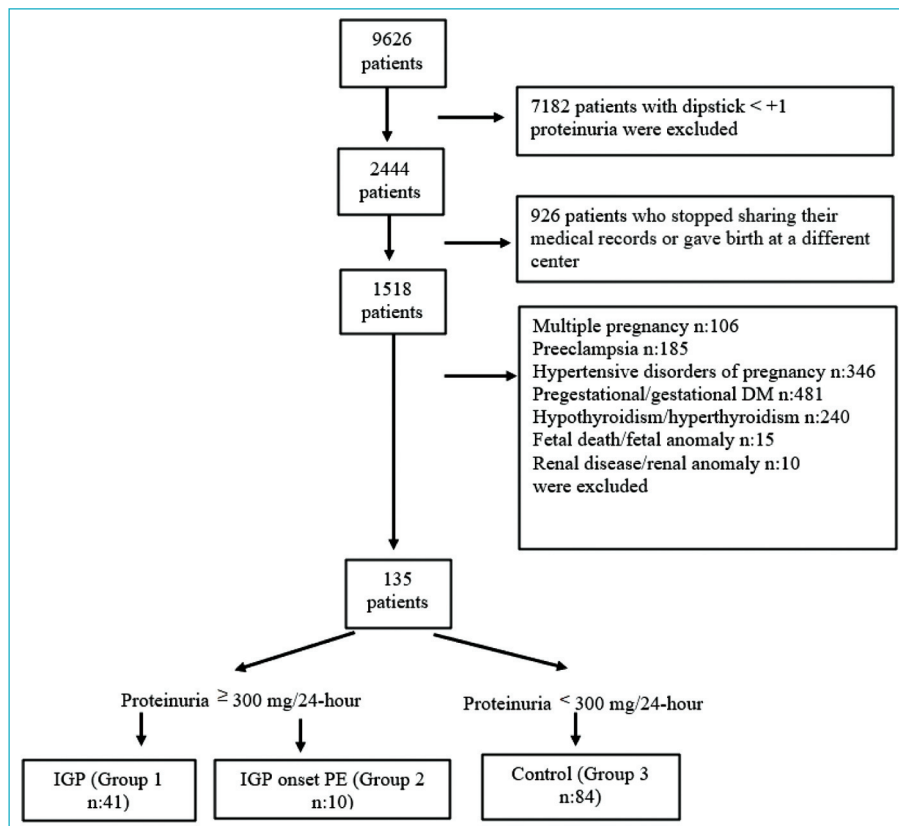


FIGURE 1: Flow chart of participants.

IGP: Isolated gestational proteinuria; PE: Preeclampsia.

ceeding 300 mg per day until delivery. All participants underwent regular monitoring, including complete blood count, biochemistry panels, and repeat 24-hour urine tests as necessary.

URINE COLLECTION PROTOCOL

Detailed instructions were provided to pregnant women on how to collect 24-hour urine samples. They were advised to avoid exercise and intercourse during the collection period. The first morning urine was discarded, and all subsequent urine was collected in a laboratory-provided container. We assessed the adequacy of urine collection by measuring urine creatinine excretion, considering a range of 11-25 mg/kg as adequate, and by using the weight measured at the time of specimen collection.¹⁵ The urine specimens were promptly processed within an hour of their arrival at the laboratory. To ascertain the total protein concentrations in the 24-hour urine specimens, we calculated the product of the total urine volume (mea-

sured in deciliters, dL) and the total urine protein concentration (expressed in milligrams per deciliter, mg/dL).

DEFINITION OF TERMS USED IN THIS STUDY

PE, as outlined in the ACOG report, is characterized by the sudden onset of hypertension, accompanied by either proteinuria or end-organ dysfunction, occurring after 20 weeks of gestation in a woman who was normotensive before this period.⁸ Gestational hypertension is defined as elevated blood pressure appearing after the 20th week of gestation in the absence of proteinuria. HELLP is a combination of hemolysis, elevated liver enzymes, and low platelet count.⁸ Eclampsia is the onset of seizures or coma in a preeclamptic woman without preexisting neurological conditions.⁸ GDM was diagnosed using abnormal values obtained from the 100-g oral glucose tolerance test after a 50-g oral glucose load of ≥ 140 mg/dL, and these cases were excluded.¹⁶ Low birth weight

(LBW) is defined as a birth weight less than 2,500 g, and a small for gestational age (SGA) baby has a birth weight below the 10th percentile according to gestational age.^{17,18} Preterm deliveries, recorded in the study, refer to births occurring prior to 37 weeks of gestation.¹⁹ Body mass index (BMI) is calculated as the ratio of weight (kg) to height (m²) and is categorized based on World Health Organization definitions, which include underweight (<18.5 kg/m²), normal (18.5-24.9 kg/m²), overweight (25.0-29.9 kg/m²), and obese (\geq 30.0 kg/m²).

STATISTICAL ANALYSIS

The data underwent statistical analysis using SPSS version 22.0 (IBM Corporation, Armonk, New York, US). Normality distribution of variables was assessed through the Kolmogorov-Smirnov test for sample sizes greater than 30 and the Shapiro-Wilk test for sample sizes less than 30. Normally distributed variables were subjected to analysis of variance (ANOVA), while non-normally distributed variables were analyzed using the Kruskal-Wallis test. Categorical variables were evaluated using the chi-square or Fisher's exact tests. Binary logistic regression analysis was employed to identify factors associated with PE, with results reported as odds ratios (OR) and 95% confidence intervals (CI). A p value <0.05 was considered statistically significant. A power analysis was conducted using G*Power 3.1.9.6 (University of Dusseldorf, Dusseldorf, Germany) to determine the required sample size for the study. The analysis aimed to ensure the study has sufficient power to detect a medium effect size (Cohen's $d=0.5$) with an 80% probability ($1-\beta=0.80$). Accordingly, it was found that there should be at least 34 participants in the IGP and control groups.

RESULTS

The study included 51 pregnant women with proteinuria of \geq 300 mg/24 hours. Of these, 41 women (80.4%) did not develop hypertension during the antenatal period and were categorized as the IGP group (Group 1), while 10 women (19.6%) developed hypertension later in pregnancy, forming the IGP onset PE group (Group 2). A control group (Group 3) was created by matching healthy preg-

nant women without proteinuria and hypertension, based on age and gestational week. Table 1 provides the demographic characteristics, obstetric, and perinatal outcomes of all participants. No significant differences were observed among the three groups in terms of maternal age, parity, adolescent pregnancy rates, advanced maternal age ratio, pre-pregnancy and prenatal BMI, weight gain during pregnancy, smoking status, and previous cesarean section history.

The mean gestational age at the time of proteinuria diagnosis was 31.2 \pm 3.2 weeks in Group 1 and 30.1 \pm 2 weeks in Group 2 ($p=0.330$). The mean 24-hour proteinuria levels were 600 \pm 654 mg in Group 1, 473 \pm 286 mg in Group 2, and 189 \pm 57 mg in Group 3. No significant difference in proteinuria levels was observed between Groups 1 and 2 (Figure 2); however, the proteinuria levels in both groups were significantly higher than those in Group 3 ($p<0.001$). In Group 2, the mean gestational age diagnosis of proteinuria was 30.1 \pm 2, the mean gestational age diagnosis of PE was 33.6 \pm 3.4 weeks. The mean interval between proteinuria and PE is 3.6 \pm 2.5 weeks. The interval between proteinuria diagnosis and delivery was 7.1 \pm 3.3 weeks for Group 1 and 5.6 \pm 3 weeks for Group 2, with no significant difference ($p=0.288$).

Group 2 had a significantly higher history of previous PE compared to Groups 1 and 3 ($p<0.001$). No significant differences were noted between Groups 1 and 3 in terms of history of previous PE, gestational age at delivery, preterm deliveries, early preterm deliveries, delivery mode, birth weight, rates of LBW infants, neonatal intensive care unit (NICU) admissions. As expected, cesarean deliveries, preterm deliveries, early preterm deliveries, LBW infants, and NICU admission rates were statistically higher in Group 2 compared to Groups 1 and 3. In Group 2, SGA infant is proportionally higher (20%) but not statistically significant, whereas gestational age at delivery and birth weight were significantly lower ($p<0.001$ and $p=0.014$, respectively).

Laboratory findings are shown in Table 2. Laboratory parameters, including complete blood count, fasting blood glucose, and liver function tests, were similar across groups. However, creatinine levels

TABLE 1: Demographic characteristics, obstetric and perinatal outcomes.

	IGP (Group 1, n=41)	IGP onset PE (Group 2, n=10)	Control (Group 3, n=84)	p value
Maternal age (years) ($\bar{X}\pm SD$)	29 \pm 5	28 \pm 6	28 \pm 6	0.843
Adolescent pregnancy \leq 19 (years) (n, %)	1 (2.4)	1 (10)	4 (4.7)	0.567
Advanced maternal age \geq 35 (years) (n, %)	8 (19.5)	1 (10)	13 (15.4)	0.725
Parity (n, %)				0.381
Nulliparous	12 (29.3)	3 (30)	16 (19)	
Multiparous	29 (70.7)	7 (70)	68 (81)	
Weight gain during pregnancy (kg) ($\bar{X}\pm SD$)	11.6 \pm 5.2	12.7 \pm 7.6	10.5 \pm 5	0.349
BMI before pregnancy (kg/m ²) ($\bar{X}\pm SD$)	26.5 \pm 5.7	28 \pm 5.4	25.3 \pm 4.7	0.181
BMI before delivery (kg/m ²) ($\bar{X}\pm SD$)	30.6 \pm 8	32.8 \pm 4.9	29.3 \pm 4.5	0.060
Smoking (n, %)	9 (22)	3 (30)	13 (15.5)	0.425
Previous cesarean section (n, %)	17 (41)	7 (70)	37 (44)	0.251
History of preeclampsia (n, %)	3 (7.3)	6 (60)	2 (2.4)	<0.001 ^{ab}
Gestational age diagnosis of proteinuria (weeks) ($\bar{X}\pm SD$)	31.2 \pm 3.2	30.1 \pm 2	-	0.330
Proteinuria (mg/24-hour) ($\bar{X}\pm SD$)	600 \pm 654	473 \pm 286	189 \pm 57	<0.001 ^{b,c}
Gestational age diagnosis of preeclampsia (weeks) ($\bar{X}\pm SD$)	-	33.6 \pm 3.4	-	-
Time interval between proteinuria and preeclampsia (weeks) ($\bar{X}\pm SD$)	-	3.6 \pm 2.5	-	-
Time interval between proteinuria and delivery (weeks) ($\bar{X}\pm SD$)	7.1 \pm 3.3	5.6 \pm 3	-	0.288
Delivery mode (n, %)				0.002 ^{ab}
Vaginal delivery	13 (46.4)	0	39 (31.7)	
Cesarean section	28 (53.6)	10 (100)	45 (68.3)	
Gestational age at birth (weeks) ($\bar{X}\pm SD$)	38.3 \pm 2.3	36.1 \pm 1.7	38.7 \pm 1.4	<0.001 ^{ab}
Preterm delivery (<37 weeks) (n, %)	6 (14.6)	5 (50)	8 (9.5)	0.002 ^{ab}
Late preterm delivery (34-37 weeks) (n, %)	5 (12.2)	3 (30)	6 (7.1)	0.073
Early preterm delivery (<34 weeks) (n, %)	1 (2.4)	2 (20)	2 (2.3)	0.017 ^{ab}
Birth weight (g) ($\bar{X}\pm SD$)	3266 \pm 675	2716 \pm 712	3233 \pm 447	0.014 ^{ab}
LBW (<2,500 g) (n, %)	3 (7.3)	5 (50)	5 (6)	<0.001 ^{ab}
SGA (n, %)	2 (4.9)	2 (20)	3 (3.6)	0.085
APGAR score <7 at 1st minute (n, %)	3 (7.3)	1 (10)	5 (6)	0.871
APGAR score <7 at 5th minute (n, %)	1 (2.4)	0	0	0.315
NICU admission (n, %)	8 (19.5)	7 (70)	9 (10.7)	<0.001 ^{ab}

^aThe difference between Group 1 and Group 2 is significant; ^bThe difference between Group 2 and Group 3 is significant; ^cThe difference between Group 1 and Group 3 is significant; IGP: Isolated gestational proteinuria; PE: Preeclampsia; BMI: Body mass index; LBW: Low birth weight; SGA: Small for gestational age; NICU: Neonatal intensive care unit; SD: Standard deviation.

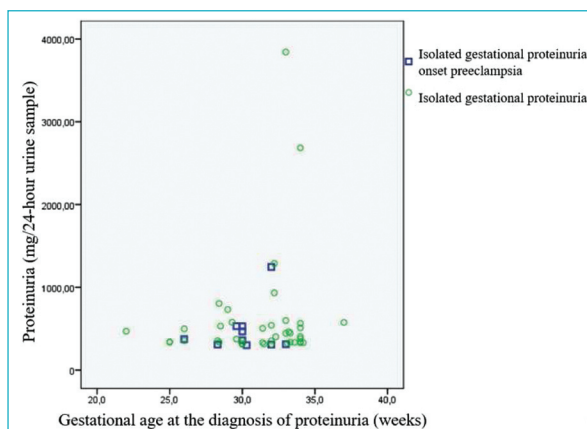


FIGURE 2: Gestational age at diagnosis and the amount of proteinuria in patients with IGP and IGP onset preeclampsia.
IGP: Isolated gestational proteinuria.

were significantly higher in Group 2 compared to the other groups ($p=0.001$).

Risk factors for PE in patients with IGP are shown in [Table 3](#). In logistic regression analysis, younger maternal age ($p=0.040$) and previous PE history ($p<0.001$) were found as risk factors in the progression of IGP to PE. The incidence of IGP in this study population was 0.53% (51 out of 9,626), approximately 1 in 190 pregnancies. The progression rate of IGP to PE was 19.6% (10/51). The overall prevalence of PE in the general study population was 2.04% (195 out of 9,520). Based on these findings, IGP was associated with a 12-fold increased risk of developing PE (OR 11.6, 95% CI 5.7-23.6; $p<0.001$).

TABLE 2: Laboratory findings.

	IGP (Group 1, n=41)		IGP onset PE (Group 2, n=10)		Control n=84 (Group 3, n=84)		p value
	Mean	SD	Mean	SD	Mean	SD	
WBC ($10^9/mm^3$) ($\bar{X}\pm SD$)	10.6	2.2	10.7	2.2	10.17	2.3	0.531
NEU ($10^3/mm^3$) ($\bar{X}\pm SD$)	7.8	1.9	7.6	1.7	7.39	1.9	0.519
LYM ($10^3/mm^3$) ($\bar{X}\pm SD$)	2	0.4	2.2	0.5	1.95	0.5	0.468
HGB (g/dL) ($\bar{X}\pm SD$)	11.4	1.1	11.6	1.2	11.33	1.1	0.764
MCV (μm^3) ($\bar{X}\pm SD$)	86.6	5.4	87.2	4.8	86.23	6.5	0.871
MCH (pg) ($\bar{X}\pm SD$)	29.4	2.2	29.7	2.2	29.13	2.7	0.780
PLT ($10^3/mm^3$) ($\bar{X}\pm SD$)	242.3	52	227.6	50.7	219.26	63.9	0.132
MPV (μm^3) ($\bar{X}\pm SD$)	8.8	1	8.8	1.0	9.05	1.1	0.354
PDW (%) ($\bar{X}\pm SD$)	17.4	0.7	17.2	0.7	17.44	0.6	0.423
Fasting blood glucose (mg/dL) ($\bar{X}\pm SD$)	91	12	88	12	87.83	11	0.335
ALT (U/L) ($\bar{X}\pm SD$)	14	6	17	17	11.86	5	0.075
AST (U/L) ($\bar{X}\pm SD$)	16	4	17	9	15.60	4	0.680
Urea (mg/dL) ($\bar{X}\pm SD$)	15	4	18	4	14.83	4	0.125
Creatinine (mg/dL) ($\bar{X}\pm SD$)	0.61	0.09	1.70	3.16	0.61	0.11	0.001 ^{a,b}

^aThe difference between Group 1 and Group 2 is significant; ^bThe difference between Group 2 and Group 3 is significant; IGP: Isolated gestational proteinuria; PE: Preeclampsia; WBC: White blood cell; NEU: Neutrophil; LYM: Lymphocyte; HGB: Hemoglobin; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; PLT: Platelet; MPV: Mean platelet volume; PDW: Platelet distribution width; ALT: Alanine transaminase; AST: Aspartate aminotransferase.

TABLE 3: Risk factors for preeclampsia in patients with isolated gestational proteinuria.

	OR 95% CI	p value
Maternal age	0.706 (0.507-0.984)	0.040
History of preeclampsia	36 (7.645-169.529)	<0.001

OR: Odds ratios; CI: Confidence intervals.

DISCUSSION

The nature of IGP has been a subject of debate, with questions about whether it represents a variant of PE or a distinct entity related to subclinical renal disease in pregnancy.^{1,2} Our study highlights the significant prevalence of PE among women with IGP, with 19.6% (10/51) of these individuals progressing to PE. This contrasts sharply with the overall PE prevalence of 2.04% (195/9,520) in the broader study population. Perhaps the most striking revelation from our study is the extent to which IGP elevates the risk of PE. We found that IGP increased the risk of PE approximately 12 times (OR 11.6, 95% CI 5.7-23.6; $p < 0.001$). Furthermore, we identified younger maternal age and previous PE history as key risk factors for the progression of IGP to PE. Importantly, our study revealed that as long as hypertension does not develop,

maternal and perinatal outcomes in women with IGP are similar to those in healthy pregnant women. To our knowledge, this is the first prospective case-control study to comprehensively compare the outcomes of women with IGP to those of healthy controls.

In 2008, Morikawa et al. first defined IGP in the literature. Their study reported favorable pregnancy outcomes in the IGP group.¹² The multicenter retrospective study of Holston et al. was the largest series in the literature with 108 nulliparous pregnant women.²⁰ In this study, it was reported that IGP is a benign condition, poor obstetric outcomes are rare, and as long as hypertension does not develop, it is not different from healthy pregnant women in terms of gestational period, preterm delivery rates, mean birth weight, incidence of SGA fetuses, perinatal death, and the need for NICU.²⁰ Our study's results align with these previous findings, highlighting that, in the absence of hypertension, pregnant women with IGP exhibit maternal and perinatal outcomes similar to those of healthy pregnant women.

Morikawa et al. also investigated the timing of proteinuria in IGP onset PE, reporting that proteinuria began at 31.1 ± 5.0 weeks, with PE occurring at 33.2 ± 4.7 weeks, leaving a 2.1 ± 1.7 week interval.¹² In

our study, proteinuria onset occurred slightly earlier (30.1 ± 2.0 weeks), with PE developing at 33.6 ± 3.4 weeks, providing a longer interval of 3.6 ± 2.5 weeks. This interval is of paramount importance as preeclamptic women are potentially predisposed to serious complications such as abruptio placentae, disseminated intravascular coagulation, hepatic failure, and acute renal failure.¹² Therefore, this interval is very valuable in terms of early diagnosis and management of PE and its complications in pregnant women with IGP.

Ekiz et al. reported lower birth weights and fifth-minute Apgar scores in the IGP onset PE group, as well as high rates of adverse perinatal outcomes, including fetal growth restriction (FGR), preterm premature rupture of membranes, placental abruption, and NICU admissions.²¹ In our study, we similarly observed lower birth weights in the IGP onset PE group. We found highest prevalence of preterm labor (<37 weeks), early preterm labor (<34 weeks), LBW infants (50%), and NICU admission rate (70%) in the IGP onset PE group (Group 2). However, there were no significant differences in the rates of SGA infants or Apgar scores between the groups.

Historically, proteinuria has been considered a “late finding” in the clinical progression of PE. Morikawa et al. presented a contrasting viewpoint, arguing that new-onset proteinuria (IGP) is actually an “early finding” in PE. Furthermore, they postulated that pregnant women with IGP are at a high risk of progressing to full-blown PE, making IGP a valuable predictor for this condition. Their study reported that among 37 pregnant women with IGP, a remarkable 51.4% (19/37) went on to develop PE.¹² To the best of our knowledge, this rate stands as the highest reported in the literature. In other studies, the progression rate from IGP to PE has been documented at 22%-34%.²¹⁻²³ In our study, we found the rate of progression of IGP to PE as 19.6%. This supports the notion that IGP is indeed a significant risk factor for PE.²² Additionally, we found that IGP increased the risk of developing PE by approximately 12 times. Some reports suggest that the risk of PE increases 13-fold in women with IGP, a finding that aligns closely with our results.²³ Erkenekli et al. reported that in pregnant women with IGP who developed PE, pro-

teinuria commenced early, and systolic blood pressure was notably higher. These two parameters were identified as contributors to the increased risk of PE.²⁴ Shinar et al. delved into risk factors associated with the progression to PE, highlighting the significance of the amount of proteinuria and its increase during pregnancy.²² Additionally, they argued that risk factors for IGP may differ from those for PE, pointing to factors like maternal age, PE history, nulliparity, and multiple pregnancies. In contrast to Shinar et al.’s findings, our study revealed that younger maternal age and previous PE history increase the risk of progression to PE in pregnant women with IGP.²²

Some researchers have hypothesized that the levels of circulating angiogenic factors in IGP are similar to those found in PE, suggesting that IGP might be considered a milder variant of PE.²⁰ Supporting this perspective, Holston et al. discussed the pathogenesis of IGP, highlighting an imbalance in the secretion of placental-derived angiogenic factors that results in an antiangiogenic dominance in maternal serum. In cases of IGP, antiangiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin tend to rise in the maternal circulation approximately two weeks before the onset of proteinuria. In contrast, placental growth factor (PlGF), a proangiogenic factor, typically decreases about 6–8 weeks before proteinuria appears.²⁰ In the existing literature, studies have reported that the levels of PlGF and sFlt-1 in pregnant women with IGP fall somewhere in between the levels observed in healthy pregnant women and those with PE.^{25,26} This suggests that the pathogenesis of IGP and PE might share similarities, with varying levels of angiogenic factors contributing to different clinical presentations (PE or IGP).²⁵ However, no studies have specifically investigated the sFlt-1/PlGF ratio in IGP to redefine the risk of PE. Other research, such as Villalain et al.’s study, has indicated that an sFlt-1/PlGF ratio exceeding 655 is almost always associated with rapidly progressing PE or FGR.²⁷ Similarly, Stepan et al. demonstrated that the sFlt-1/PlGF ratio is a valuable tool for predicting both early- and late-onset PE during the second and third trimesters.²⁸ Zeisler et al. further noted that an sFlt-1/PlGF ratio of 38 or below can be used to predict the short-term absence of PE.²⁹

Although we were unable to investigate these angiogenic markers in our study, our findings do show an increased rate of PE in women with IGP, supporting the need for further research into the role of angiogenic factors in predicting PE in this population.

STRENGTHS AND LIMITATIONS

To the best of our knowledge, this study represents the first prospective examination of maternal and perinatal outcomes in pregnant women with IGP. However, it's important to acknowledge certain limitations. The single-center nature of the study limits its external validity and generalizability to a broader population. Perhaps the most notable constraint is the relatively small sample size, underscoring the need for larger prospective studies to validate and build upon our results. Previous reports indicate that the incidence of IGP ranges from 0.33% to 1.9%.^{21,23} In our study, we found that the incidence of IGP is 0.53%. These differences in IGP incidence may be due to differences in the study group and study design. We performed diagnosis of IGP by determining the total amount of protein in 24-hour urine, which is the gold standard. However, we screened for proteinuria using the dipstick test. This test was prone to error, and its sensitivity varies between 22%-86%, potentially leading to underdiagnosis of significant proteinuria in some cases.³⁰ In addition, although PE is known to be associated with serious maternal complications such as abruptio placenta, HELLP syndrome, maternal near-miss, we did not record any early or late neonatal mortality or severe maternal complications in our cohort.³¹ This gap in data collection was due to the limited number of patients with IGP onset PE in our sample. Despite these limitations, we believe our study offers valuable insights into IGP and highlights the importance of further research. We hope that this study encourages future prospective investigations with larger sample sizes to provide more robust data

and enhance our understanding of IGP and its role in pregnancy outcomes.

CONCLUSION

In conclusion, our findings underscore the significantly increased risk of PE in cases of IGP. This emphasizes the importance of regular and frequent antenatal follow-up for pregnant women diagnosed with IGP. Importantly, unless hypertension develops in IGP, there is no difference between maternal and neonatal outcomes in pregnant women with IGP and healthy pregnant women.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

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