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The Association Between GFR Evaluated by Serum Cystatin C and Proteinuria During Pregnancy

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Introduction: Physiological changes in pregnancy result in increased cardiac output and renal blood flow, with a consequential increase in proteinuria. Data from studies of the relationship between proteinuria caused by isolated proteinuria and glomerular filtration rate (GFR) are still limited. The objective of this study was to investigate the effects of isolated proteinuria on the cystatin C–based GFR in the third trimester of pregnancy.

Methods: Data were collected from pregnant women in their third trimester whose serum creatinine levels were normal. The GFR of each participant was measured using serum cystatin C levels, and proteinuria was measured using urine protein–creatinine ratios. The participants were divided into 3 groups according to their level of proteinuria: normal (<150 mg/d), physiological (150–300 mg/d), and gestational (>300 mg/d). Changes in GFR were recorded for each group.

Results: The study included 89 participants, of whom 66.3% had levels of proteinuria that did not differ from that of the normal population (<150 mg/d). The incidence of physiological and gestational proteinuria was 21.4% and 12.4%, respectively. The results demonstrate that proteinuria >101.50 mg/d was significantly associated with declined estimated glomerular filtration rate (eGFR) ($r = –0.34$, $P = 0.01$). The analysis found that proteinuria >491.27 mg/d led to a risk of GFR <90 ml/min with an odds ratio of 12.69, $P = 0.02$ when adjusted for systolic blood pressure (SBP), diastolic blood pressure (DBP), and body mass index.

Conclusion: This study suggests that the term "physiological proteinuria" is a misnomer. When used in the traditional manner, creatinine level has inadequate sensitivity to estimate GFR in pregnant women. We found that there is a significant decline in GFR when urine protein > 101.5 mg/d, which could be an early biomarker for renal pathology rather than pregnancy physiology, suggesting that further workup and precaution is required.

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Hemodynamic changes in pregnancy lead to physiological and anatomic adaptation of the kidneys, which increases both renal vascular and interstitial compartmental volumes, as well as the kidney size. In addition, with a rise in plasma volume and red cell volumes, the overall elevation of blood volume increases cardiac output and renal blood flow,[1] with an inclination toward consequential proteinuria and hypertension that peaks in the third trimester.[1–3]

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Whereas the normal limit of proteinuria is 150 mg/d in normal populations, because of increased blood volume and renal blood flow in pregnant women, the resulting hyperfiltration causes the gestational age–related increase in urinary protein excretion that does not exceed 300 mg/d, called physiological proteinuria (equivalent to a 1+ on a urine dipstick).[1–5] When protein excretion exceeds 300 mg/d, it is most plausibly explained by preexisting renal or glomerular disease, often presenting simultaneously with preeclampsia and hypertension. However, it has been found that certain patients have proteinuria of 300 mg/d without hypertension, which is called "isolated proteinuria without hypertension" or "gestational proteinuria." Previous studies have shown that this condition occurs in 0.3% of all pregnancies, and persons with this

condition are shown to have increased risk of preeclampsia.[6,7]

In healthy nonpregnant patients, proteinuria may affect the rate of filtration as protein leakage into tubules incurs tubular toxicity, especially of the proximal tubule, leading to renal fibrosis of the interstitial area.[8–10] If the pathology occurs in pregnant women, the consequential reduction in GFR may be the cause of hypertension that stems from the complications of renal failure. In contrast, proteinuria <300 mg/d that arises from physiological changes will not affect renal function.[11–13] Early studies used serum creatinine to evaluate GFR, a technique that has been shown to have low sensitivity and is an unreliable indicator of acute renal dysfunction in pregnant women.[14,15] Presently, the evaluation of GFR by serum cystatin C has been found to have more reliability in pregnancy, with evidence that an increase in cystatin C is indicative of acute kidney injury (AKI) in pregnancy.[16–20]

The purpose of this study is to demonstrate the association between proteinuria and GFR estimated by serum cystatin C in the third trimester pregnancies, with a new clarification of the term "physiological proteinuria."

MATERIALS AND METHODS

Clinical Data Collection

The subjects in this proscriptive cohort study were pregnant women who received antenatal care at Her Royal Highness Princess Maha Chakri Sirindhorn Medical Center, Faculty of Medicine, Srinakharinwirot University, during the period from January 20, 2016, through August 10, 2017. The sample size was calculated according to the correlation: point biserial model. The corresponding inputs used to determine the sample size were the prevalence of the categorical outcome (renal impairment of pregnancy; eGFR <90 ml/min) and the amount of proteinuria assumed by the alternative hypothesis. Type 1 error (α) was 0.05, and type 2 error (β) was 0.2.

As a result, a total sample size with margin of error was 82 cases. All the patients provided signed informed consent to participate. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Research Committee at the Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand (ethical approval No. SWUEC/E-197/2559).

The participants were 28 or more weeks into their pregnancy, with no renal disease or history of proteinuria, along with normal blood pressures and GFRs before or during the pregnancy (serum creatinine 0.4–0.8 mg/dl).[1] When a participant had urine protein >300 mg/d, a nephrologist was notified and preeclampsia and other glomerular diseases were monitored throughout the remainder of the pregnancy until term. The degree of proteinuria was measured using the urine protein–creatinine ratio[5] concurrent with 24-hour urine protein. Participants were then separated into groups according to their level of proteinuria: normal proteinuria (<150 mg/d), physiological proteinuria (150—300 mg/d), and gestational proteinuria (>300 mg/d), with SBP <140 mm Hg and DBP <90 mm Hg. All participants had normal serum creatinine levels (0.4–0.8 mg/dl), and the results also were compared with serum cystatin C–measured GFRs.

Clinical and Laboratory Evaluation

The following patient data were collected: age, gestational age, last menstrual period, number of pregnancies and abortions, diagnoses of preeclampsia before or during the study, physical examination results (including the degree of edema [if present] and blood pressure), and findings of laboratory investigations such as serum creatinine, dipstick urine for protein nitrite, urinalysis, spot urine for protein and creatinine, and serum cystatin C.

GFR values were measured with use of cystatin C, which was analyzed according to the turbidimetric/immunoturbidimetric method using the ARCHITECT ci8200 Integrated System (Abbott Laboratories, Abbott Park, IL). eGFR using serum cystatin C was calculated with use of the Chronic Kidney Disease Epidemiology Collaboration cystatin C equation (2012),[21] which is $eGFR = 133 \times \min(S_{cys}/0.8, 1)^{-0.499} \times \max(S_{cys}/0.8, 1)^{-1.328} \times 0.996^{Age} \times 0.932$.

Urine protein and urine creatinine were measured through spot midstream urine (5–10 ml) from spun urine (1500 rpm for 5–10 minutes) that was dipstick-tested nitrite negative along with <5 white blood cells per high-power field in the urinalysis.

Urine protein and urine creatinine values also were analyzed using the turbid metric method with the ARCHITECT ci8200, and the results (in milligrams per deciliter) were then calculated as a ratio to obtain the urine protein–creatinine ratio, which was then compared with the 24-hour urine protein (grams per day) and presented in this study as milligrams per day.

Participant Characteristics

Participants who met the inclusion criteria were acknowledged and advised prior to the study. Inclusion criteria were being pregnant, age >20 years, and gestational age >28 weeks. Exclusion criteria were having a high-risk pregnancy from causes such as placenta previa, gestational diabetes mellitus (GDM), or intrauterine fetal demise; having a known renal disease or a serum creatinine level >0.8 mg/dl prior to the

study; being diagnosed with preeclampsia or SBP ≥140 and/or DBP ≥90 before or during the study[22]; and suspected urinary tract infection (e.g., being feverish, having positive urine nitrite, or having a white blood cell count of >5 cells/high-power field in an unspun urine specimen).

Participants were tested for their level of urine protein and subsequently their urine protein–creatinine ratio. They were grouped according to their urine protein–creatinine ratio as follows: <150 mg/d (normal proteinuria), 150–300 mg/d (physiological proteinuria), and >300 mg/d (gestational proteinuria). Subjects subsequently diagnosed with preeclampsia were removed from the study (Figures 1 and 2).

Statistical Analysis

The statistical software package SPSS 23.0 (IBM Corp., Armonk, NY) was used for statistical analysis. Through descriptive statistics, collected data were arranged into groups in terms of both frequency and percentage. The mean value and SD were compared among the groups of continuous data with use of the Student *t*-test. The χ^2 test was then used to reveal the relationship of the continuous and categorical variables. The Spearman correlation coefficient was used to assess correlation of selection algorithms of continuous and ordinal variables. A logistic cubic regression[23] was used to interpret the directional correlation between the value of urine protein and GFR. A 2-sided *P* value <0.05 was considered statistically significant.

Theoretical Glomerular Hyperfiltration Threshold Model

As a consequence of hyperfiltration, a notable gestational age-related increase in urinary protein excretion occurs, but it rarely exceeds 300 mg/d. Theoretically, by assuming that the hyperfiltration causes proteinuria, there would be a positive correlation between GFR and proteinuria in the study. As hyperfiltration increases, so would the degree of proteinuria. However, this phenomenon occurs only until the point of reversal between GFR and proteinuria, at which time the theoretical glomerular hyperfiltration threshold is reached.[1–3] Beyond the theoretical glomerular hyperfiltration threshold, the negative correlation between GFR and proteinuria would occur (in Figure 3 in this cohort, the threshold means the peak of cubic polynomial curve). It is believed that proteinuria present beyond the threshold occurred as a result of other pathologic causes.

RESULTS

Patient Characteristics

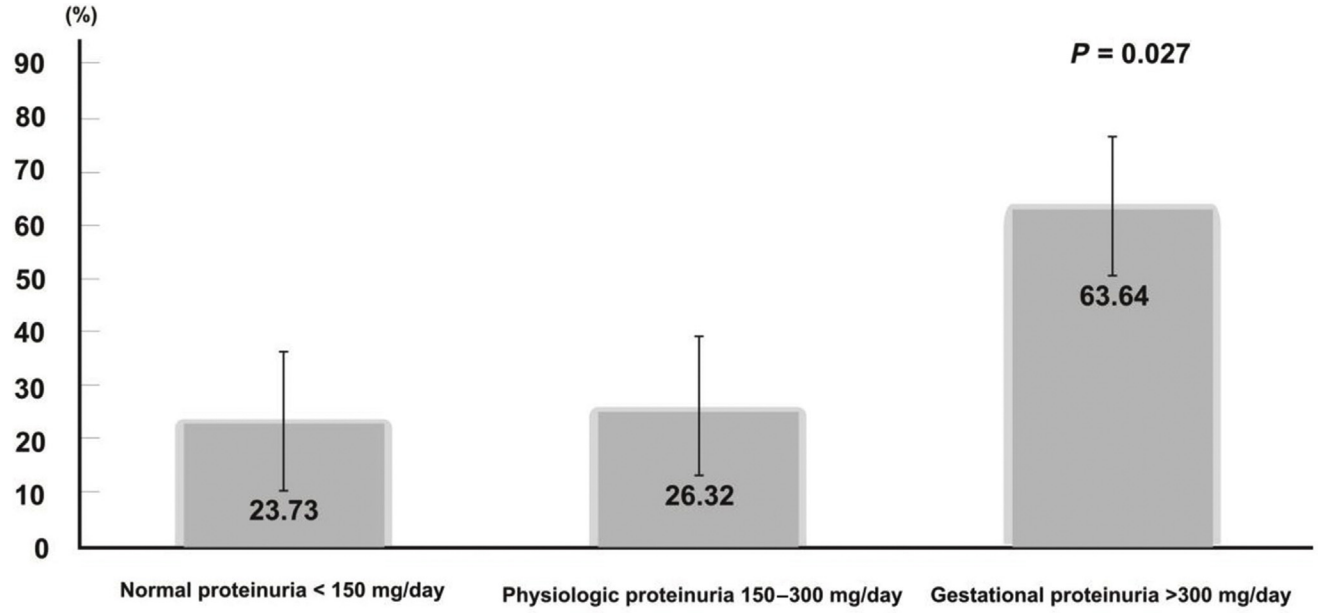
Of 93 initial participants, 4 were removed from the study because 1 participant had a serum creatinine level >0.8 mg/dl and 3 of 14 participants (21.4%) in the gestational proteinuria group were diagnosed with preeclampsia; thus the final number of participants was 89. Of the remaining participants, the average maternal age during the study was 27.47 ± 6.2 years. The average gestational age of the cohort at the time of study enrollment was 33.0 ± 1.9 weeks. The average maternal GFR calculated by a cystatin C–based formula was 96.9 ± 22.4 ml/min (minimum–maximum: 38–141 ml/min). The average maternal SBP was 121.5 ± 9.9 mm Hg (minimum–maximum: 100–140 mm Hg) and the average DBP was 74.7 ± 8.2 mm Hg (minimum–maximum: 60–90 mm Hg). The average body surface area was 1.6 ± 0.2 m^2, and the average body mass index was 24.2 ± 4.3 kg/m^2 (Table 1). The urine protein level measured by spot/random urine protein–creatinine ratio showed that 59 patients (66.3%) had normal proteinuria (urine protein <150 mg/d), 19 (21.4%) had physiological proteinuria (urine protein 150–300 mg/d), and 11 (12.4%) had gestational proteinuria (urine protein >300 mg/d) without the manifestation of hypertension or preeclampsia.

Most pregnancies (98.88%) during this study resulted in term labor; only one subject had a preterm labor in which the gestational age was 36.4 weeks. This subject had a normal proteinuria level (<150 mg/d). The average gestational age at delivery was 38.9 ± 0.8 weeks. The average birth weight was 3106.0 ± 336.7 g, and the average placental weight was 653.1 ± 117 g (Table 1).

Association Between Proteinuria and the Obstetric Outcome

Analysis of the urine protein–creatinine ratio showed that there was no clinical significant difference between maternal ages, gestational ages at evaluation, SBP and DBP, and gestational age at delivery (Table 2).

Upon examining the effects of obstetric outcomes on proteinuria, it was found that mothers with larger babies and placentas are more likely to have proteinuria. Data showed that in the group with normal proteinuria, the average baby birth weight and average placental weight was 3035.8 ± 329.9 g and 620.4 ± 107.9 g, respectively. The group with physiological proteinuria had an average baby birth weight and average placental weight of 3196.8 ± 283.1 g and 703.68 ± 115.1 g, respectively. The group with gestational proteinuria had an average baby birth weight and average placental weight of 3368.2 ± 305.7 g and 739.1 ± 105.4 g, respectively. These data showed a significance difference in average baby birth weight and average placental weight between the group with normal proteinuria



Group with proteinuria	Crude OR (95% CI)	*P* value	Adjusted OR[a] (95% CI)	*P* value
Normal proteinuria (< 150 mg/day)	Reference	1	Reference	1
Physiological proteinuria (150-300 mg/day)	1.15 (0.35, 3.75)	0.82	1.49 (0.43, 5.23)	0.53
Gestational proteinuria (> 300 mg/day)	5.63 (1.43, 22.07)	0.01[b]	5.5 (1.28, 23.73)	0.02[b]

Figure 1. Prevalence of pregnancy with renal impairment (estimated glomerular filtration rate [eGFR] <90 ml/min) and the odds of renal impairment according to level of proteinuria. The prevalence of pregnancy with renal impairment had significantly increased in the group of pregnant patients who had proteinuria (>300 mg/d) with normal blood pressure. The odds ratio (OR) of having eGFR <90 ml/min in the particular group of pregnant patients is 5.6 ($P = 0.02$) when compared with the pregnant patients who had normal proteinuria (<150 mg/d). However, there was no significant difference in the prevalence of renal impairment between the pregnancies with normal proteinuria and those with physiological proteinuria. [a]After adjusted by maternal age, body mass index, body surface area, systolic blood pressure, and diastolic blood pressure. [b]Statistically significant *P* value < 0.05. CI, confidence interval.

and the group with gestational proteinuria, but no significant difference was found between the group with physiologic proteinuria and the group with gestational proteinuria (Table 2).

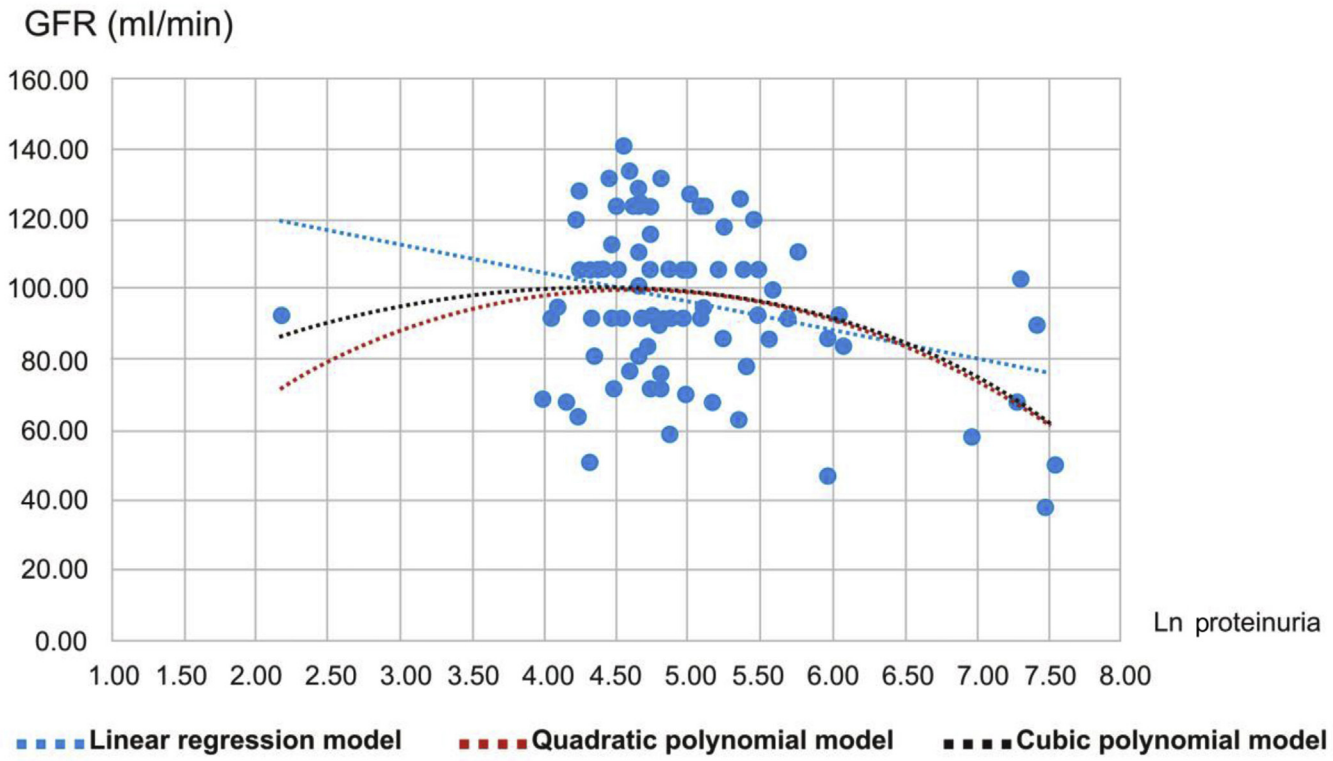
Association Between Proteinuria and GFR

In this study, the lower eGFR correlated with higher levels of proteinuria—that is, 100.1 ± 21.2 ml/min, 99.4 ± 18.5 ml/min, and 75.2 ± 24.4 ml/min for participants with normal proteinuria, physiological proteinuria, and gestational proteinuria, respectively. Significant differences were found between the gestational and normal groups with a *P* value of 0.001 and between the gestational and physiological groups with a *P* value of 0.003 (Table 2).

The pregnancy with eGFR <90 ml/min was defined as renal function impairment.[24–26] The results show that the prevalence of pregnancies with eGFR <90 ml/min was significantly higher in the group with proteinuria >300 mg/d than in the normal group and in the group with physiological proteinuria ($P = 0.03$; Figure 1).

The calculated odds ratio, showing the strength of risk association of having GFR <90 ml/min, indicated that pregnant women with proteinuria >300 mg/d had 5.5 times the odds of having a low GFR compared with women who had normal levels of urine protein ($P = 0.02$), whereas no significant difference was found when comparing the physiological and normal proteinuria groups (odds ratio = 1.49, $P = 0.53$; Figure 1).

To further evaluate the association between proteinuria and hyperfiltration, the proteinuria that was calculated using the urine protein–creatinine ratio was given a natural logarithm (Ln) to spread the data so it



Model equations:

Linear regression model: $y = -8.0778x + 137.18$, $R^2 = 0.09$

Quadratic polynomial regression model: $y = -4.7245x^2 + 43.646x$, $R^2 = 0.14$

Cubic polynomial regression model: $y = -0.3994x^3 + 2.1795x^2 + 5.0253x + 70.097$ $R^2 = 0.15$

Figure 2. Correlation between level of proteinuria and regression model. The graph demonstrated the natural logarithms (Ln) of proteinuria, which were plotted against the estimated glomerular filtration rate (eGFR). Regression analysis was used to determine the best predicting equation for the model. These results revealed that the cubic polynomial regression model ($y = -0.3994x^3 + 2.1795x^2 + 5.0253x + 70.097$) had the highest correlation for proteinuria to predict the GFR outcome ($R^2 = 0.15$, $P < 0.05$).

resembled a normal distribution as much as possible (Figure 2). It was found that the cubic polynomial regression model has the strongest correlation when compared with the linear and the quadratic polynomial models, and thus the cubic polynomial regression model was used to resemble the trend of the data (Figure 2).

The results of polynomial regression study demonstrated that the peak of the cubic curve was Ln proteinuria = 4.6, which equalized as proteinuria of 101.5 mg/d. In other words, this indicated theoretical glomerular hyperfiltration; the eGFR had a positive correlation limit of 101.5 mg/d of proteinuria (Figure 3). The regression analysis also revealed that urine protein >101.50 mg/d was significantly associated with declined eGFR ($r = -0.34$, $P = 0.01$; Figure 4). Moreover, we found that the point of cubic polynomial curve at Ln proteinuria equals 6.2, which indicates the renal impairment of pregnancy (GFR < 90 ml/min). By calculating the Ln proteinuria into the amount of protein, it is equal to 491.3 mg/d. It is shown as a blue dot in Figure 4, which corresponds to Figure 3 as the slope of the cubic polynomial curve declining rapidly beyond the point of 6.2 Ln proteinuria. The risk of renal function impairment when GFR is <90 ml/min was further analyzed using a logistic regression analysis, which found that pregnant women with urine protein >491.3 mg/d would have a risk of GFR <90 ml/min with an odds ratio of 12.7, $P = 0.02$ when adjusted for SBP, DBP, and maternal body mass index (Table 3).

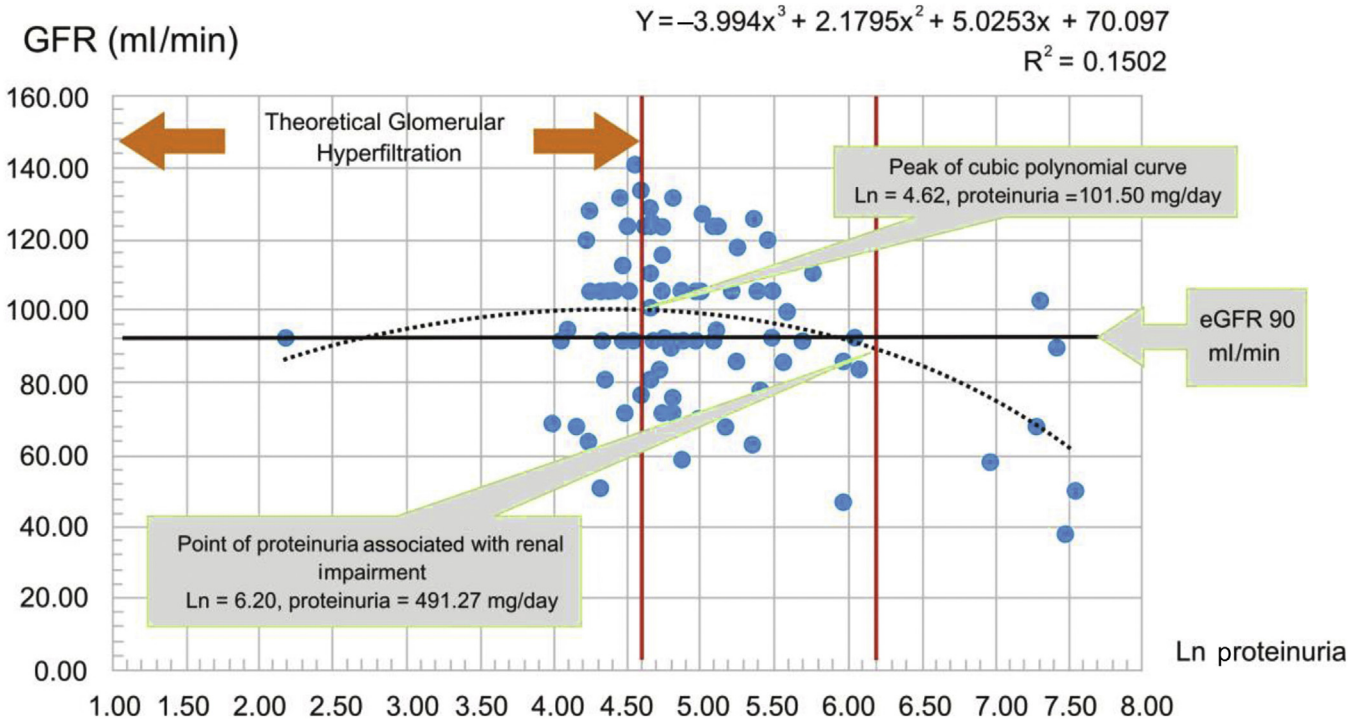


Figure 3. Correlation between level of proteinuria and estimated glomerular filtration rate (eGFR). The graph demonstrated the natural logarithm (Ln) of proteinuria, which was plotted against the eGFR. A positive correlation between proteinuria and eGFR was found, showing a hyperfiltrative state with only proteinuria <101.5 mg/day. When proteinuria was >101.5 mg/d (Ln = 4.6), GFR was found to decrease, and an increasingly inverse correlation developed, reaching the lowest GFR as proteinuria was found to be >491.3 mg/d (Ln = 6.2).

DISCUSSION

The results of this study demonstrate the possible effects of proteinuria, especially on eGFR during the third trimester of pregnancy (which is known to have the highest prevalence of proteinuria), with the exclusion of patients who have hypertension, a factor that may have been a significant confounder of the results (thus subjects with preeclampsia and those with an underlying preexisting kidney disease were omitted). The results show that proteinuria at a level of 150–300 mg/d, or what is usually called "physiological proteinuria," must have been caused by other mechanisms of pregnancy than by pregnancy itself, because the use of cystatin C did not show signs of physiological proteinuria.

Table 1. Clinical characteristics of pregnant women

Pregnancy characteristics	Mean ± SD
Maternal age (yr)	27.5 ± 6.2
Maternal BMI (kg/m^2)	24.2 ± 4.3
Maternal BSA (m^2)	1.6 ± 0.2
Overall proteinuria, $n = 89$, g (minimum–maximum)	238.1 ± 372.8 (8.8–1896.3)
Normal proteinuria (150 mg/d), $n = 59$, g (minimum–maximum)	99.4 ± 27.4 (8.8–149.4)
Physiological proteinuria (150–300 mg/d), $n = 19$, g (minimum–maximum)	211.7 ± 39.1 (160.8–294.4)
Gestational proteinuria (>300 mg/d), $n = 11$, g (minimum–maximum)	1027.7 ± 644.5 (318.5–1896.3)
Maternal SBP (mm Hg)	121.5 ± 9.9
Maternal DBP (mm Hg)	74.7 ± 8.2
Serum cystatin C level (mg/dl)	1.0 ± 0.2
Cystatin C–based GFR (ml/min)	96.9 ± 22.4
Gestational age at evaluation (wk)	33.0 ± 1.9
Gestational age at delivery (wk)	38.9 ± 0.8
Baby birth weight (g)	3106.0 ± 336.7
Placental weight (g)	653.1 ± 117

BMI, body mass index; BSA, body surface area; DBP, diastolic blood pressure; GFR, glomerular filtration rate; SBP, systolic blood pressure.

It has been suggested that proteinuria can cause AKI and, subsequently, the eGFR. The fundamental argument this article is trying to illustrate is that physiological proteinuria is certainly physiological without any eGFR effects. Cystatin C was selected as a marker of AKI instead of serum creatinine to promptly detect AKI in pregnancy.[27]

The results of this study demonstrate the association of proteinuria with GFR and obstetric outcomes in the third trimester of pregnancy with 3 main findings: (i) there exists a hyperfiltration during pregnancy that may not, however, result in a proteinuria that exceeds the normal limit; (ii) proteinuria that is more than the upper limits may be associated with a decline in GFR when assessed with an early AKI biomarker such as cystatin C; and (iii) therefore, physiological proteinuria may not result from physiological changes in pregnancy but rather from pathologic changes that both increase proteinuria and decrease GFR. It can be considered as a consequence of pathologic or physiological change

Table 2. Association among the group of proteinuria, clinical relevance, and obstetric outcome

Clinical relevance	A[a] (<150 mg/d), N = 59	B[b] (150–300 mg/d), N = 19	C[c] (>300 mg/d), N = 11	P value		
				A vs. B	A vs. C	B vs. C
Antenatal characteristic (mean ± SD)						
Maternal age, yr	27.4 ± 6.2	26.6 ± 7.3	29.6 ± 4.2	0.63	0.29	0.21
Gestational age at evaluation, wk	32.9 ± 1.7	33.7 ± 1.8	32.7 ± 2.7	0.11	0.71	0.15
Maternal BMI, kg/m^2	24.2 ± 4.3	23.3 ± 3.7	25.4 ± 4.8	0.42	0.42	0.21
Maternal BSA, m^2	1.6 ± 0.2	1.6 ± 0.2	1.7 ± 0.2	0.08	0.65	0.10
Maximum SBP, mm Hg	120.8 ± 10.6	122.2 ± 7.4	124.5 ± 9.9	0.60	0.26	0.54
Maximum DBP, mm Hg	73.9 ± 8.1	77.5 ± 8.0	74.6 ± 9.3	0.09	0.80	0.34
eGFR, ml/min	100.1 ± 21.2	99.4 ± 18.5	75.3 ± 24.4	0.89	<0.01[d]	<0.01[d]
Obstetric outcome, mean ± SD						
Placental weight, g	620.4 ± 107.9	703.7 ± 115.1	739.1 ± 105.4	<0.01[d]	<0.01[d]	0.39
Baby birth weight, g	3035.8 ± 329.9	3196.8 ± 283.1	3368.2 ± 305.7	0.04[e]	<0.01[d]	0.16
Gestational age at delivery, wk	38.9 ± 0.8	39.3 ± 0.8	38.8 ± 0.7	0.06	0.98	0.09

BMI, body mass index; BSA, body surface area; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.
[a]Normal proteinuria.
[b]Physiological proteinuria.
[c]Gestational proteinuria.
[d]Statistical significant *P* value < 0.01.
[e]Statistically significant *P* value < 0.05.

during pregnancy. The effect on obstetric outcomes may depend on the primary cause that occurred during pregnancy.

Past studies showed that the physiological change that occurs during pregnancy is capable of inducing an increased proteinuria, called physiological proteinuria, especially in the third trimester of pregnancy. The resulting hyperfiltration causes a gestational age–related increase in urinary protein excretion, which does not exceed 300 mg/d. The increase in hyperfiltration aggravates proteinuria until a certain point when a reversal occurs between GFR and proteinuria correlation as the glomerular hyperfiltration threshold is reached. The negative correlation between GFR and

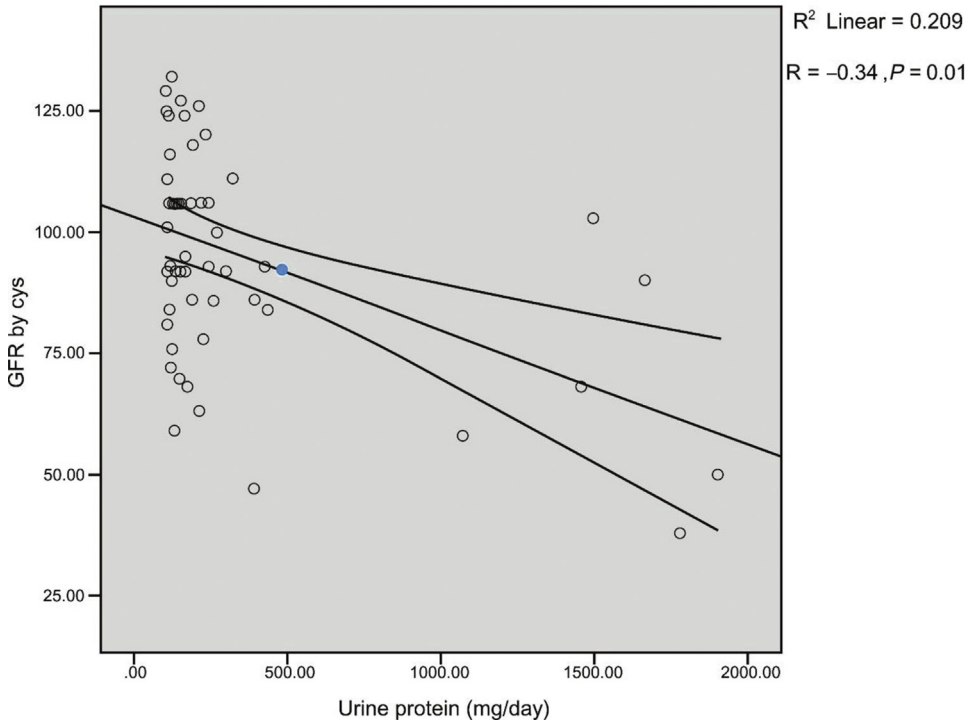


Figure 4. Correlation between estimated glomerular filtration rate (eGFR) and proteinuria when urine protein-to-creatinine ratio >101.5 mg/d. The linear regression line appears as the line in the middle, with the confidential intervals of the mean as the upper and lower lines. A significant negative correlation between the amount of proteinuria with >101.5 mg/d and eGFR (R = –0.34, *P* = 0.01) is found. The blue dot indicates the proteinuria level of 491.3 mg/d, with the regression analysis showing it as a significant risk of renal impairment (eGFR <90 ml/min). cys, cystatin C.

Table 3. Risk evaluation of proteinuria associated with renal impairment (GFR <90 ml/min)

Urine protein >491.27 mg/d	eGFR <90 ml/min (OR, 95% CI)	*P* value
Univariate	13.0 (1.45, 117.74)	0.01
Multivariate	12.7 (1.29, 125.10)	0.02[a]

CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.
[a]After adjusted by systolic blood pressure and diastolic blood pressure.

proteinuria (Figure 3, the peak of cubic polynomial curve) would have occurred from other pathological causes.

In this study, however, it was found that the majority of pregnant women (66.3%) had levels of proteinuria that did not differ from the normal population (<150 mg/d), with the incidence of physiological and gestational proteinuria being 21.4% and 12.4%, respectively.

Positive correlation was found between proteinuria and cystatin C–based GFR only at the beginning of the cubic curve. This positive correlation continued through the proteinuria level of approximately 100 mg/d. When proteinuria increased beyond 101.5 mg/d, however, it was found that the level of GFR significantly decreased, indicating a negative correlation (Figure 4). It can be said that the glomerular hyperfiltration state found in pregnancy might not exceed normal limits (> 150 mg/d) when GFR was estimated by cystatin C (Figure 3).

These findings show that the higher level of proteinuria during pregnancy that in previous studies[2,13,24,27–30] was thought to have stemmed from physiological changes may have been the result of aggravation of preexisting renal disease. This outcome may have been due to the fact that creatinine was not a sensitive biomarker to detect AKI, especially during pregnancy. With the definition of physiological proteinuria as proteinuria that did not affect GFR levels and that may increase up to 300 mg/d, a more thorough implication may be required to avoid misdiagnosis of occult renal or glomerular diseases that may be aggravated by pregnancy and also associated with AKI. Furthermore, the results of gestational proteinuria, especially in patients with high protienuria (> 491.3 mg/d) without hypertension, are also at risk for renal impairment (GFR <90 ml/min). Our results demonstrated that when proteinuria increased to >491.3 mg/d, patients have 12 times the risk of having a GFR <90 ml/min when compared with patients who have lower levels of proteinuria. Approximately 21.4% of patients with gestational proteinuria will have preeclampsia in the late period of gestational age. According to a previous study, approximately 13% to 33% of patients with gestational proteinuria will have preeclampsia in the late period of gestational age.[6,31,32] It is possible that the occurrence of gestational proteinuria with a decrease in GFR is the initial pathologic response to preeclampsia.

Our findings also show that proteinuria levels are likely to increase in mothers who have overweight newborns and placentae. Contrary to most previous reports, patients with very high proteinuria had a lower GFR, which eventually can be associated with intrauterine growth restriction and low birth weight.[33–36] The argumentative explanation in this finding is a result of this research. This study was conducted in patients without preeclamptic proteinuria, stipulating that the cause of proteinuria in this disease must have alternate explanations other than the imbalance between angiogenic and anti-antigenic factors linking placental ischemia/hypoxia with microvascular dysfunction,[37–39] resulting in IUGR as found in preeclampsia. On the other hand, the biomarker report found that the level of serum cystatin C correlates with the risk of having GDM[40,41] and that GDM is associated with infant weight. It is possible that the physiological proteinuria as a result of hyperfiltration may have a relationship with GDM,[42,43] which may present the association between proteinuria and higher baby weight that we found in this report. Further studies should be conducted to determine the relationship between GDM and proteinuria.

Limitations and Suggestions

In this study we performed only a single measurement of cystatin C level. Therefore, it cannot be proved that these patients had AKI or chronic kidney disease as an intrinsic factor contributing to proteinuria. Thus a longitudinal study in which serial measurement of cystatin C-based GFR is performed will result in better insight about the association between proteinuria and GFR (normal or hyperfiltration) in pregnancy.

Kidney biopsy is not routinely used to prove the cause of proteinuria > 300 mg/d in pregnant patients who can possibly have preexisting renal disease prior to pregnancy because the physiological excessive proteinuria and gestational proteinuria, which is the early spectrum of preeclampsia, could be found in the pregnancy. An increase in the research population number may increase the power of the study. Along with GDM, gestational proteinuria would also be further studied for effects on eGFR based on early AKI biomarkers. GDM might cause the reduction of GFR by itself, which is a hypothesis that must be further investigated. Moreover, a study with a larger sample size in the longitudinal study format with samples from the first trimester to the third trimester also must be further investigated.

DISCLOSURE

All the authors declared no competing interests.

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