KI REPORTS
KIReports.org

Isolated Proteinuria of Pregnancy: A Call for Action

Ranine Ghamrawi[1], Andrea G. Kattah[1] and Vesna D. Garovic[1]

[1]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA

Kidney Int Rep (2019) **4,** 766–768; https://doi.org/10.1016/j.ekir.2019.04.012

See Clinical Research on Page 854

Pregnancy is associated with physiological adaptations that facilitate meeting the increased metabolic demands and appropriate growth and development of the fetus. Various systems and organs are affected, including the kidneys and urinary system. Kidneys enlarge with progression of pregnancy (on average, by 1 cm) and this enlargement is accompanied by glomerulomegaly and dilation of the collecting system. The sum effect of volume expansion, increases in cardiac output and pulse rate, reduced systemic vascular resistance, and systolic and diastolic blood pressures is renal vasodilation and increased renal plasma flow (RPF) early in pregnancy. This is considered a major contributor to the hyperfiltration and increase in glomerular filtration rate (GFR) observed during pregnancy. This results in lower levels of serum creatinine levels, from a mean of 0.7 to 0.5 mg/dl, although pregnancy-specific creatinine values are not known.[1] The hyperfiltration combined with the reduction of tubular reabsorption is thought to increase urine protein excretion, making the threshold for proteinuria in pregnant subjects (up to 300 mg/24 hours) higher than in nonpregnant subjects (up to 150 mg/24 hours). However, the relationship between proteinuria and GFR in pregnancy is unknown.

In this issue of *KI Reports*, Kreepala *et al.*[2] studied the relationship between isolated proteinuria and cystatin C–based GFR (Cys-GFR) in the third trimester of pregnancy. They conducted a prospective cohort study in pregnant women receiving antenatal care at Her Royal Highness Princess Maha Chakri Sirindhorn Medical Center, Srinakharinwirot University, Thailand, between January 2016 and August 2017. They included pregnant women who were 28 or more weeks into their pregnancies, with no known renal disease or proteinuria, with normal blood pressures (systolic blood pressure <140 and diastolic blood pressure <90 mm Hg) and with normal renal function before or during the pregnancy (serum creatinine 0.4–0.8 mg/dl). They assessed proteinuria by measuring the urine protein-creatinine ratio concurrent with 24-hour urine protein. The participants were divided into 3 groups: normal proteinuria (<150 mg/d), physiologic proteinuria (150–300 mg/d), and gestational proteinuria (>300 mg/d). Eighty-nine participants were included in the study, with a mean age of 27.5 years and an average Cys-GFR of 96.9 ml/min. The authors found that as protein excretion increased, the GFR gradually increased up to a threshold of 101.50 mg/d, after which increased proteinuria was associated with a gradual decline in GFR ($r = -0.34$, $P = 0.01$). They also found that proteinuria >300 mg/d was associated with a higher risk of a GFR <90 ml/min, which is considered to indicate significant renal impairment (odds ratio of 5.5, $P = 0.02$). The results remained significant after adjustments for systolic blood pressure, diastolic blood pressure, and body mass index.

Elevated proteinuria in pregnancy has been reported in several studies[3–5] and has been considered, for the most part, to be physiological. We have previously reported that both albuminuria and proteinuria increase from the beginning of pregnancy up to delivery, whereas clinically significant proteinuria (>300 mg/d) was identified in 13.4% of normotensive pregnancies. Similarly, an increase in GFR and RPF was also noted in very early studies of kidney function during pregnancy.[5,S1] These clinical observations can be associated mechanistically with known hemodynamic changes that occur with pregnancy (Figure 1). Notably, it is believed that a surge in relaxin causes an increase in renal nitric oxide production, thus triggering renal vasodilation and a decrease in renal afferent and efferent arteriolar resistance.[1,6] Resultant increase in RPF leads to

Correspondence: Vesna D. Garovic, Division of Nephrology and Hypertension, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905, USA. E-mail: garovic.vesna@mayo.edu

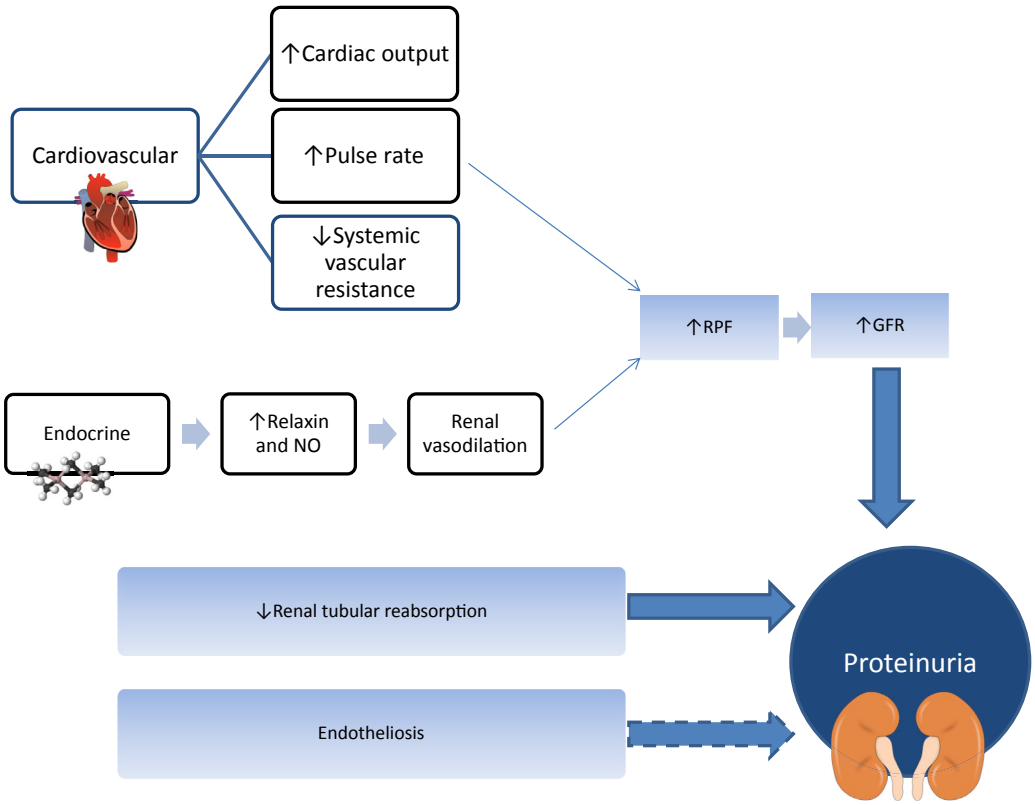

Figure 1. Possible mechanisms generating proteinuria in normotensive pregnancies. The sum effect of increases in cardiac output and pulse rate, reduced systemic vascular resistance, and renal vasodilation is increased renal plasma flow (RPF) early in pregnancy, resulting in an increase in glomerular filtration rate (GFR). This increase in GFR combined with the decrease in renal tubular reabsorption cause proteinuria. Endotheliosis could also play a role in proteinuria in normotensive pregnancies. ↑, increase; NO, nitric oxide.

a higher single-nephron and whole-kidney GFR.[5] Consequently, the glomerular hyperfiltration and injury have been extensively studied with respect to physiological proteinuria of normal pregnancy and proteinuria that occurs with pregnancy complications (such as preeclampsia). An increase in antiangiogenic factors and the resulting endothelial dysfunction, in the form of endotheliosis, has been described in renal lesions of preeclampsia, and has been considered to be the underlying cause for both proteinuria and decrease in GFR. In turn, these changes also have been reported in up to 12% of normal pregnancies, thus offering a possible mechanism for proteinuria that occurs during uncomplicated pregnancies. In addition, impaired tubular reabsorption also may contribute to the generation of proteinuria. Although hyperfiltration may play a role in increased protein excretion, there is a paucity of data connecting GFR changes and protein excretion in pregnancy. This highlights the importance of the current study, in which hyperfiltration alone does not seem to explain the proteinuria seen in pregnancy. The use of Cys-GFR for assessment of kidney function in pregnancy may be advantageous, as Cys-GFR is a reliable marker of GFR that is superior to that of creatinine.[S2] However, few studies conducted during pregnancy have evaluated kidney function using Cys-GFR.

It is important to note that Larsson *et al.*[7] reported that in healthy pregnant women, Cys-GFR was higher than estimated GFR-MDRD (modified diet in renal disease) in the first 2 trimesters and lower in the third trimester and before delivery. The decline in Cys-GFR seen with a greater amount of proteinuria in the third trimester might, in part, be due to the inherent nature of Cys-GFR testing. In a recent study,[8] we reported that cystatin C levels in (expressed as mean ± SD) were significantly increased in 49 women with preeclamptic pregnancies (1.44 ± 0.35 mg/l) compared with 42 women with normotensive pregnancies (1.21 ± 0.27 mg/l) at the time of delivery; however, cystatin C levels in the latter group were higher than expected based on the group's creatinine average (0.62 ± 0.13 mg/dl). A recent study also found that cystatin C was higher in twin gestations than in singleton pregnancies.[9] As cystatin C is produced by all nucleated cells, it is possible that increases in cystatin C in the third trimester and in twin

gestations may be due to increased placental and fetal mass, as opposed to true changes in GFR. Taken together, these findings identify the need for a comparative analysis of serial creatinine and cystatin measurements during normal and complicated pregnancies. The current study also underscores the importance of revisiting the ranges of protein excretion considered to be normal in pregnancy. One would not expect a decline in GFR with normal protein excretion levels. In fact, it might be argued that the occurrence of proteinuria during pregnancy might be the first manifestation of underlying subclinical kidney disease.

The results of this study should be interpreted within the context of limitations that may have an impact on the study's ability to evaluate the true significance of proteinuria and GFR changes observed during pregnancy. As mentioned appropriately by the authors, the sample size was small, gestational diabetes mellitus was not accounted for, and no kidney biopsies were performed on pregnant patients with a significant decline in GFR and elevated proteinuria. The pregnant patients were all evaluated during the third trimester with no assessments of their prior creatinine values, GFRs, or proteinuria in the prior trimesters, or before pregnancy. The lack of longitudinal follow-up does not allow for determination as to whether the changes truly occurred during the third trimester of pregnancy, or were present prior.

Despite its limitations, the study by Kreepala *et al.*[2] reports several findings that highlight the importance of pregnancy-specific normal values for the definition of proteinuria and impaired kidney function. It also highlights deficiencies in understanding physiological alterations affecting the kidneys. As such, the current study sets the stage for future studies that should address the gaps existing in the knowledge of renal adaptations in healthy pregnancies. Larger population-based studies with longitudinal follow-up and adequate power are needed to study the glomerular filtration process and the handling of protein by the kidneys during pregnancy. In the end, some crucial questions arise: What should be considered physiologic proteinuria? What are the potential unknown factors that are contributing to its development? And, are we perhaps missing the opportunity for early detection of an underlying predisposition to develop future kidney disease? Let's embrace these challenges.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

This study was supported by R01HL 136348 (Vesna D. Garovic) from the National Heart, Lung, and Blood Institute.

SUPPLEMENTARY MATERIAL

Supplementary References.

Supplementary material is linked to the online version of the paper at www.kireports.org.

REFERENCES

1. Leveno K. *Williams Obstetrics. 25th Edition*. New York: McGraw-Hill Education; 2018.
2. Kreepala C, Srila-on A, Kitporntheranunt M, et al. The association between GFR evaluated by serum cystatin C and proteinuria during pregnancy. *Kidney Int Rep*. 2019;4:854–863.
3. American College of Obstetricians and Gynecologists. Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol*. 2013;122:1122–1131.
4. Kattah A, Milic N, White W, Garovic V. Spot urine protein measurements in normotensive pregnancies, pregnancies with isolated proteinuria and preeclampsia. *Am J Physiol Regul Integr Comp Physiol*. 2017;313:R418–R424.
5. Odutayo A, Hladunewich M. Obstetric nephrology: renal hemodynamic and metabolic physiology in normal pregnancy. *Clin J Am Soc Nephrol*. 2012;7:2073–2080.
6. Conrad K, Davison J. The renal circulation in normal pregnancy and preeclampsia: is there a place for relaxin? *Am J Physiol Renal Physiol*. 2014;306:F1121–F1135.
7. Larsson A, Palm M, Hansson L, Axelsson O. Cystatin C and modification of diet in renal disease (MDRD) estimated glomerular filtration rate differ during normal pregnancy. *Acta Obstet Gynecol Scand*. 2010;89:939–944.
8. Gilani SI, Anderson UD, Jayachandran M, et al. Urinary extracellular vesicles of podocyte origin and renal injury in preeclampsia. *J Am Soc Nephrol*. 2017;28:3363–3372.
9. Peng J, Wang W, Zheng L, et al. Serum cystatin C levels in twin pregnancy versus singleton pregnancy. *Lab Med*. 2019;50:163–167.