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Editorial Comment

EDITORIAL COMMENT

Baseline proteinuria level and adverse outcomes in pregnant women with chronic kidney disease: new evidence and a note of caution

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ABSTRACT

About 3% of all pregnancies occur in patients with some degree of chronic kidney disease (CKD) and, in turn, CKD is a risk factor for developing hypertensive disorders of pregnancies (HDP) and unfavorable pregnancy outcomes, at both the maternal and fetal level. CKD is often characterized by proteinuria and proteinuria is a risk factor for HDP. However, even if the positive correlation between proteinuria and unfavorable pregnancy outcomes is well acknowledged, the degree of proteinuria associated with adverse outcomes is still a matter of debate. In this issue of the Journal, Li *et al.* present a retrospective study that shows that >1 g of proteinuria/day is associated with worse maternal outcomes while >2 g/day with worse fetal ones. This study gives proteinuria thresholds for unfavorable outcomes in pregnant CKD patients, but it should be kept in mind that there is a linear correlation between proteinuria and worse pregnancy outcomes, thus a strict surveillance during the entire gestation should be advised independently of the proteinuria level.

Keywords: CKD, hypertensive disorders of pregnancy, preeclampsia, preterm birth, small for gestational age

About 3% of all pregnancies occur in patients with some degree of chronic kidney disease (CKD) [1]. Pregnant women with CKD represent a group of patients with higher risks of adverse maternal and fetal outcomes [1–4]. However, this group is not homogenous and can be further defined by several characteristics such as CKD stage, CKD etiology or proteinuria, etc. How each of these parameters influences maternal and fetal outcomes is of interest. Indeed, we need to identify risk factors of both maternal adverse outcomes (in particular preeclampsia) and fetal adverse outcomes such as fetal and neonatal death, preterm delivery and low birth weight, in order to provide better pre-conceptional counselling, to adapt pregnancy monitoring and to offer preventive therapeutic strategies. Finally, stratifying the risk of adverse outcomes integrating several parameters with thresholds for each parameter would be clinically useful.

Proteinuria is a common finding in all CKD stages, particularly as a diagnostic feature of glomerular diseases, but can be detected at lower levels in other kidney diseases. Albuminuria can even be detected earlier than proteinuria, it is diagnostic of CKD if >30 mg/day when present for >3 months and has been included in the CKD risk stratification by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines since 2012 [5]. Proteinuria is associated with CKD progression and patient death. Early reduction of proteinuria or albuminuria is associated with slower progression of kidney disease [6, 7]. Thus, we can define proteinuria and albuminuria as diagnostic, prognostic and

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predictive biomarkers in CKD. Detection of proteinuria before pregnancy or during the first semester of pregnancy is usually associated with kidney disease [8]. On the other hand, proteinuria detected after 20 gestational weeks can be related to both kidney disease and/or preeclampsia.

The hypertensive disorders of pregnancy (HDP) complicate up to 15% of all pregnancies [9]. They represent an heterogeneous group of diseases encompassing gestational hypertension, preeclampsia, superimposed preeclampsia and the hemolysis, elevated liver enzymes, low platelets syndrome (HELLP) [10]. Recently, our understanding of these diseases has evolved: HDP are no longer considered self-resolving with delivery but they have been shown to represent a risk factor for developing future kidney disease [11]. This vicious cycle impacts the health of reproductive-age women and it is even more relevant if we consider that HPD affect, in absolute terms, more than 18 million women every year and may turn into a substantial burden of non-communicable diseases in the future [12]. HDP are associated with several risk factors such as antiphospholipid antibody syndrome, a previous history of preeclampsia, chronic hypertension, diabetes mellitus, obesity and medically assisted reproduction [13]. Moreover, any degree of CKD has long been known to be a risk factor for developing preeclampsia and, in general, HDP [2, 14] and CKD affect between 0.1% and 4% of women of reproductive age [15–17]. Historically, pregnancy was discouraged in patients with CKD but, fortunately, in recent decades the number of pregnancies in CKD patients with favorable outcomes has increased [18–20]. Since the first observations, proteinuria has been one of the main features of preeclampsia, and, even if it is no longer mandatory in order to establish the diagnosis, it is still included in every preeclampsia definition [10, 21].

Proteinuria before or early in pregnancy ("baseline" proteinuria) is associated with worse outcomes, both maternal [4] and fetal [2, 4]. However, is there a baseline proteinuria threshold able to predict fetal or maternal adverse outcomes in pregnant women with CKD?

In this issue of the Journal, Li and colleagues try to answer to this question [22]. The authors analyzed 570 pregnancies in 557 women affected by CKD in terms of severe preeclampsia, early preterm birth, stillbirth, fetal–neonatal death, very low birth weight (VLBW) and small for gestational age. The authors divided patients according to their first trimester proteinuria into five groups: (i) <300 mg/day (controls), (ii) 0.30–1 g/day, (iii) 1–2 g/day, (iv) 2–5 g/day and (v) ≥5 g/day. Some 16.34% of the enrolled patients were on immunosuppressive therapy (including steroids). Causes of kidney disease were mostly glomerular, but more than half of the patients did not have kidney biopsy. Overall, 19.3% of patients presented chronic hypertension. Most patients had stage 1 CKD (71.99%) and the proportion of more advanced stages decreased from stage 2 (18.85%) to stage 5 (0.36%). Regarding maternal outcomes, they report that proteinuria >1 g/day at baseline was associated with the development of preeclampsia in the mother in multivariate analysis (as well as hypertension, but not CKD stage). Regarding fetal outcomes, they report in multivariate analysis the association of a proteinuria level >2 g/day with VLBW (i.e. <1500 g) and early preterm delivery of the infant (i.e. <34 gestational weeks), and proteinuria >5 g/day with fetal or neonatal death, while CKD stage was only associated with early preterm birth.

Despite the absence of a non-CKD control group, this large cohort of pregnant women gives us an insight into the continuum of maternal and fetal adverse outcomes risks with higher proteinuria levels, independently of CKD stage, in a population including mostly CKD stage 1 women (i.e. women without glomerular filtration rate impairment). An important point is that, despite the authors' conclusions, an increased risk for severe preeclampsia was already present in women with proteinuria between 0.3 and 1 g/day [odd ratio (OR) 5.87 in the univariate analysis, OR 4.90 in the multivariable analysis], suggesting that any baseline level of proteinuria may adversely affect pregnancy. This should draw the attention of clinicians, as preventive strategies for preeclampsia such as aspirin could be useful in this population [23].

The impact of proteinuria level on maternal and fetal adverse outcomes has mostly been studied during preeclampsia, i.e. evaluating the level of proteinuria at the time of preeclampsia. Furthermore, most of these studies focused on patients without preexisting CKD. It has been shown that there is an increasing risk for adverse maternal outcomes as proteinuria increases at any given age at time of preeclampsia [24]. Nonetheless, up to 20% of patients who develop preeclampsia may have an undiagnosed underlying CKD [14]. Much fewer studies have focused on the relationship between baseline (i.e. associated with preexisting kidney disease) proteinuria and adverse pregnancy outcomes. Piccoli *et al.* described a higher risk of adverse neonatal outcomes with higher CKD stage in a large cohort (including non-CKD controls), with baseline proteinuria >1 g/day associated with adverse neonatal outcomes in CKD stage 1 women [2]. In a meta-analysis, Zhang *et al.* showed a higher incidence of preeclampsia in women with proteinuria greater than 0.5 g/day compared with women presenting proteinuria between 0 and 300 mg/day [4]. Thus, Li *et al.*'s study adds evidence to the prognostic value of baseline proteinuria in pregnancy. Of note, in the cohort reported by Li and colleagues, baseline proteinuria was measured during the first trimester of pregnancy and not before conception.

Li *et al.* performed a further comparison between patients under steroids or immunosuppressive agents or not. Compared with patients on immunosuppressive therapy, untreated patients had lower proteinuria values in the first trimester (0.25 vs 0.83 g/day), probably as a result of a less aggressive underlying disease. Steroids/immunosuppressive therapy was not associated with adverse pregnancy outcomes in the multivariate analysis. It is difficult to draw conclusions regarding this parameter, as therapy may be associated with more aggressive and/or active disease and further information regarding the type of immunosuppressive therapies and disease duration are lacking.

Moreover, Li *et al.* did not consider the evolution of proteinuria during pregnancy. Pregnancy may trigger the progression/worsening of the underlying kidney disease, thus conferring a greater risk of adverse pregnancy outcomes, especially in more advanced CKD stages or with greater proteinuria [2, 25, 26]. Finally, the study does not provide information on albuminuria, which may be useful to better predict the cardiovascular risk of the mother and the risk of CKD progression as highlighted in patients with diabetic and non-diabetic CKD [7, 27]. In this respect, further studies are warranted and may help standardize the evaluation of patients in obstetrics as is already suggested for cardiology patients, for whom the most recent guidelines have adopted albuminuria to stratify the cardiovascular risk [28].

Overall, the study by Li *et al.* provides further insight into the prognostic value of proteinuria, at all stages of CKD, for both maternal and fetal outcomes. This advocates for assessment of proteinuria before or early in pregnancy for women with known kidney diseases or risk factors for kidney disease. We believe that a careful follow-up of women with CKD is mandatory during pregnancy, regardless of proteinuria levels. Ideally, a multidisciplinary team should be in charge of the follow-up, with, at least, a gynecologist, a nephrologist, a midwife, a dietician and a psychologist [29]. The underestimation of even the smallest

evident risk factor may compromise the outcome of pregnancy and we cannot take this risk with our beloved patients and their babies.

CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Li et al. Twenty-four-hour proteinuria levels are associated with adverse pregnancy outcomes among women with CKD. *Clin Kidney J* (2023) 16: 1634–1643.)

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