

# Infertility and Pregnancy Loss in Hispanic/Latino Women with Chronic Kidney Disease: Results from the Hispanic Community Health Study/ Study of Latinos (HCHS/SOL)

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## Research article

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# Abstract

**Background:** Hispanic/Latino individuals are less likely to receive optimal treatment for chronic kidney disease (CKD) than non-Hispanic whites. This may be particularly detrimental for women of reproductive age as CKD may increase risk for infertility, menstrual irregularities, and pregnancy loss. While these maternal outcomes have been associated with advanced CKD, their occurrence in mild to moderate CKD is unclear.

**Methods:** Using baseline (2008-2011) and second study visit (2014-2017) data from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), we assessed the association between CKD and self-reported infertility, cessation of menses, hysterectomy, and nonviable pregnancy loss (experienced at less than 24 weeks gestation) in women of reproductive age (18-45 years). Multivariable survey logistic regression analyses were used to compute prevalence odds ratios with 95% confidence intervals (OR, 95% CI).

**Results:** Of the 2,589 women included (mean age 31.4 years), 4.6% were considered to have CKD. In adjusted analyses, women with CKD did not have a significantly increased odds of infertility (OR 1.02, 95% CI 0.42 - 2.49), cessation of menses (OR 1.25, 95% CI 0.52 - 3.04) or hysterectomy (OR 1.17, 95% CI 0.61 - 2.25) compared to those without CKD. In those with CKD, the adjusted odds of a nonviable pregnancy loss was increased when considering pregnancies occurring after baseline visit (OR 2.11, 95% CI 0.63 - 7.02) but not statistically significance.

**Conclusion:** In our Hispanic/Latino cohort, the presence of mild to moderate CKD did not confer an additional risk of our outcomes of interest. Examining nonviable pregnancy loss after CKD diagnosis in a larger sample warrants further study.

## Background

Impaired fertility, menstrual irregularities, and early menopause have been commonly described in women with advanced chronic kidney disease (CKD) including those on dialysis. These conditions are thought to be related to uremic toxins and an altered gonadal axis, resulting in hyperprolactinemia and a reduced cyclic surge of luteinizing and follicle stimulating hormones.[1–4] Women with end-stage kidney disease (ESKD) appear to have higher rates of early pregnancy loss.[5] While this may in part be related to higher rates of comorbid conditions such as obesity, diabetes, and hypertension, a uremic milieu likely also plays a role.[6–9] The threshold of kidney impairment and/or proteinuria at which a woman's risk of these conditions substantially increases is currently unknown. Likewise, the prevalence of impaired fertility, cessation of menses and early pregnancy loss in women with mild to moderate CKD has not been well described.

Hispanic/Latinos in the United States (U.S). are less likely to be screened for kidney disease risk factors or receive optimal treatment for CKD after diagnosis.[10, 11] They account for a nearly 40% higher prevalence rate of ESKD than non-Hispanic whites and may experience increased risk of progression to ESKD.[12][13] In the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), a prospective study of over 16,000 individuals throughout the U.S., the prevalence of CKD in all women (aged 18–74 years) was 13% and disease unawareness for men and women combined reached 18%.[14] Given the above, disease unawareness and lack of treatment could be particularly detrimental for Hispanic/Latino women of reproductive age. Indeed, minority women in the U.S. are disproportionately affected by the rising rates of early pregnancy loss.[15, 16]

To uniquely assess the impact of mild to moderate CKD on fertility and early pregnancy loss in a high-risk cohort, we performed a secondary analysis of data from the HCHS/SOL baseline (2008–2011) and second study visit (2014–  
Loading [MathJax]/jax/output/CommonHTML/jax.js of CKD in Hispanic/Latino women of reproductive age (18–45 years old)

as well as the separate associations between CKD and infertility, cessation of menses, hysterectomy (as a marker for abnormal uterine bleeding), and nonviable pregnancy loss (experienced at less than 24 weeks gestation).

## Methods

### Study population

The HCHS/SOL is a population-based cohort of 16,415 Hispanic/Latinos aged 18–74 years from 9,872 randomly selected households in four U.S. field communities (Bronx, New York; Chicago, Illinois; Miami, Florida; and San Diego, California). The sample design and cohort selection have been previously described.[17, 18] Briefly, a stratified two-stage area probability sample of household addresses was selected in each community. The first sampling stage randomly selected census block groups with stratification based on Hispanic/Latino concentration and proportion of high/low socioeconomic status. The second sampling stage randomly selected households, with stratification, from U.S. Postal Service registries that covered the randomly selected census block groups. Sampling weights were generated to reflect the probabilities of selection at each stage.

At the baseline visit (2008–2011), 4,119 women were in the reproductive age range defined as ages of 18–45 years old. Of these, 2,810 women returned for a second study visit between 2014 and 2017. Women were eligible for the present analysis if they provided serum and/or urine samples at both visits (for CKD determination) and completed the reproductive and medical history questionnaire administered at the second study visit (n = 2,589).

The HCHS/SOL study adheres to the Declaration of Helsinki and was approved by the institutional review boards at each field center where all participants gave written consent at each study visit.

### Data collection

Each study visit included clinical measurements, fasting venous blood collection and spot urine specimens. Participants were asked to bring all current medications to each visit. Questionnaires were used to obtain information on demographic factors, acculturation, medical, and social history. At the second visit, all women were asked to complete a reproductive and medical history questionnaire and a pregnancy complication questionnaire (see Additional file 1 and 2 for included questionnaires). The information obtained from these questionnaires included events occurring both before and after the baseline visit.

### Exposure Assessment

Serum creatinine was measured on a Roche Modular P Chemistry Analyzer using a creatinase enzymatic method (Roche Diagnostics, Indianapolis, IN) and was isotope dilution mass spectrometry traceable. Urine albumin was measured using an immunoturbidimetric method on the ProSpec nephelometric analyzer (Dade Behring GmbH, Marburg, Germany). Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation from serum creatinine, gender, age and race (black or non-black).[19] CKD was typically defined by either a low eGFR ( $< 60$  ml/min per  $1.73$  m<sup>2</sup>) or a urine albumin to creatinine ratio (UACR) of  $> 30$  mg/g on spot urine samples at both visits. However, given our younger cohort and noted variability in measurements from two visits, we expanded our definition of CKD to include the following: a) if a participant's eGFR was  $< 60$  ml/min per  $1.73$  m<sup>2</sup> at one visit and  $< 70$  ml/min per  $1.73$  m<sup>2</sup> at another, b) if a participant's UACR was  $> 300$  mg/g (considered macroalbuminuria/ severely increased albuminuria) at either visit, and c) if at baseline visit, a participant's UACR  $> 30$  mg/g while taking an angiotensin converting enzyme-inhibitor (ACE-I) or angiotensin receptor blocker (ARB) and  $< 30$  mg/g at the subsequent visit. In our primary analysis, we utilized this broader definition of

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CKD. A sensitivity analysis in which we limited our definition to only those with a low eGFR ( $< 60$  ml/min per  $1.73$  m<sup>2</sup>) or UACR  $> 30$  mg/g at both visits was also performed.

## Outcome Assessment

In the reproductive questionnaire, infertility was assessed with the question, “Have you ever tried to become pregnant for greater than one year without success?” and women were also asked to report the perceived cause of their infertility (medical problem in themselves, their partner, or both). Cessation of menses was assessed (“Have your natural periods stopped permanently?”) as well as the reason why it occurred. All women were asked to report a history of hysterectomy. Women reported their total number of pregnancies and how many occurred before or after the baseline visit. Early pregnancy losses occurring before the baseline visit were specified as miscarriage vs tubal/ectopic vs elective termination (derived) but were combined as pregnancies lasting less than 24 weeks in the administered survey when occurring after baseline visit (see Additional file 1).

## Covariates

Covariates from the baseline visit included age, body mass index (BMI), hypertension and diabetes. Each study visit collected the participant’s date of birth, standing height and weight. Hypertension was defined as a sitting systolic blood pressure  $\geq 140$  mmHg, diastolic blood pressure  $\geq 90$  mmHg, or use of an antihypertensive medication (documented or self-reported use of an antihypertensive medication). Diabetes mellitus was defined as fasting plasma glucose of  $\geq 126$  mg/dl, 2-hour post-load glucose levels of  $\geq 200$  mg/dl, a hemoglobin A1c level of  $\geq 6.5\%$ , or self-reported diabetes.

## Statistical Analyses

Summary statistics, prevalence estimates, and odds ratios were weighted to adjust for sampling probability and nonresponse.[17, 18] All analyses account for cluster sampling and the use of stratification in sample selection. Survey-specific procedures were used in all analyses to account for the two-stage sampling design, stratification, and clustering. Descriptive statistics including mean  $\pm$  standard deviation and counts and percentages were employed to characterize differences among women with CKD versus those without. Bivariate analysis included Chi-square tests for categorical variables and adjusted Wald tests for continuous variables. We used survey logistic regression analyses to determine the unadjusted and multivariable-adjusted associations between CKD and the separate outcomes of infertility, cessation of menses, hysterectomy and nonviable pregnancy loss (less than 24 weeks gestation). A sensitivity analysis restricted the definition of CKD to women with either a low eGFR ( $< 60$  ml/min per  $1.73$  m<sup>2</sup>) or a UACR of  $> 30$  mg/g at both visits ( $n = 96$ ).

Due to the limited number of outcome events, we assessed the influence of potential confounders one at a time to ensure model convergence. Covariates considered included participant’s age, BMI, presence of diabetes and hypertension at baseline study visit. For each study outcome, we used a 10% change in estimate approach for final covariate selection. Prevalence odds ratios and their 95% confidence intervals (OR, 95% CIs) were computed. All statistical tests were two-sided with a significance level of 0.05. Analyses were performed using Stata software (version 15.1; StataCorp LLC, College Station, TX, USA).

## Results

### Study Cohort Characteristics

A total of 2,580 women met study selection criteria and were included in the analysis (Figure 1).

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Abbreviations: CKD, chronic kidney disease; HCHS/SOL, Hispanic Community Health Study, Study of Latinos

Of these individuals, 120 (4.6%) women were classified as having CKD according to our primary definition. Table 1a displays the characteristics of the study cohort at the baseline study visit, both overall and stratified by CKD status. The mean age was  $31.4 \pm 8.3$  years old and most women (44.3%) identified their heritage/ethnicity as Mexican, followed by Cuban (14.5%) and Puerto Rican (12.7%). Compared to those without CKD, women with CKD were older ( $35.1$  vs  $31.2$  years old) and had a higher BMI ( $33.4 \text{ kg/m}^2$  vs  $29.3 \text{ kg/m}^2$ ). Fewer women with CKD had received a high school diploma or more compared to those without CKD (65.7% vs 73.1%). Women with CKD had over three times the prevalence of diabetes (25.5% vs 7.0%) and over four times the prevalence of hypertension (30.7% vs 6.7%) compared to those without CKD. The average time between baseline and second study visit was 6.2 years for both groups.

**Table 1**

**a. HCHS/SOL Baseline Visit (2008-2011) Characteristics of All Reproductive Age Women and by CKD status**

Characteristic	Overall n = 2,589	Without CKD n = 2,469	With CKD n = 120
*Age (years)	$31.4 \pm 8.3$	$31.2 \pm 8.3$	$35.1 \pm 7.7$
*BMI ( $\text{kg/m}^2$ )	$29.5 \pm 7.1$	$29.3 \pm 7.1$	$33.4 \pm 7.4$
Heritage/Ethnicity (%)			
Central American	8.1	7.9	12.6
Cuban	14.5	14.7	9
Dominican	11.4	11.4	10.5
Mexican	44.3	44.1	47.3
Puerto Rican	12.7	12.6	14.6
South American	4.3	4.5	1
More than one	4.7	4.7	5
High school diploma or more (%)	72.8	73.1	65.7
Cigarette use (past or current) (%)	23.3	23.3	22.1
Alcohol use (past or current) (%)	77.6	77.8	74.3
*Diabetes (%)	7.8	7.0	25.5
*Hypertension (%)	7.8	6.7	30.7
Average systolic BP (mmHg)	$108.5 \pm 12.4$	$108.2 \pm 12.0$	$115.9 \pm 18.3$
Average diastolic BP (mmHg)	$68.6 \pm 10.1$	$68.3 \pm 9.8$	$74.8 \pm 14.1$
ACE-I/ARB at baseline visit (%)	3.5	2.7	20.2
Creatinine (mg/dL)	$0.70 \pm 0.1$	$0.70 \pm 0.1$	$0.76 \pm 0.3$
	$111.7 \pm 16.2$	$112.0 \pm 15.7$	$104.2 \pm 24.7$
*Estimated GFR ( $\text{mL}/\text{min}/1.73\text{m}^2$ )			
*Urine albumin to creatinine ratio (mg/g)	6.7 (4.8-11.3)	6.5 (4.7-10.5)	77.6 (42.1- 284.7)

\*Statistically significant ( $p < 0.05$ ) difference between women without CKD and women with CKD

Data are mean  $\pm$  standard deviation or percent except for urine albumin to creatinine ratio which is median (interquartile range)

Abbreviations: HCHS/SOL, Hispanic Community Health Study, Study of Latinos; BMI, body mass index; BP, blood pressure; ACE-I/ARB, angiotensin converting enzyme inhibitor/ angiotensin II receptor blocker; GFR, glomerular filtration rate

The majority (67.5%) of women with CKD met criteria for CKD based only on an elevated UACR at both visits while 12.5% met criteria due to a persistent eGFR < 60 ml/min/1.73 m<sup>2</sup> or a combination of elevated UACR and low eGFR. An additional 20% were considered to have CKD through one of the expanded definitions. The median (interquartile range) UACR of those with CKD at the baseline visit was 77.6 (42.1- 284.7) mg/g and was 123.8 (36.4- 493.9) mg/g at the second visit compared to 6.5 (4.7–10.5) mg/g and 4.1 (2.5–7.9) mg/g at baseline and second visit in those without CKD (Table 1b).

Table 1  
b. HCHS/SOL Second Study Visit (2014–2017) Kidney Characteristics of All Reproductive Age Women and by CKD status

Characteristic	Overall n = 2,589	Without CKD n = 2,469	With CKD n = 120
Time between baseline visit and second visit (years)	6.2 ± 0.9	6.2 ± 0.9	6.2 ± 1.0
Creatinine (mg/dL)	0.65 ± 0.2	0.65 ± 0.1	0.75 ± 0.6
*Estimated GFR (mL/min/1.73 m <sup>2</sup> )	111.9 ± 13.8	112.3 ± 13.0	104.1 ± 24.3
*Urine albumin to creatinine ratio (mg/g)	4.4 (2.6-9.0)	4.1 (2.5–7.9)	123.8 (36.4- 493.9)

\*Statistically significant (p < 0.05) difference between women without CKD and women with CKD

Data are mean ± standard deviation or percent except for urine albumin to creatinine ratio which is median (interquartile range)

Abbreviations: HCHS/SOL, Hispanic Community Health Study, Study of Latinos; GFR, glomerular filtration rate

## CKD and infertility, cessation of menses, and hysterectomy

Infertility was reported by 15.0% of women with CKD and 12.8% of women without CKD. Of those who responded to a follow-up question of the perceived cause of their infertility (n = 142), all women with CKD reported their infertility was due to either a medical problem in themselves or both themselves and their partner (vs. their partner alone). A small percentage of women without CKD (7.5%) reported their infertility was due to their partner alone. Cessation of menses was reported by 26.7% of women with CKD and 14.5% of women without CKD at similar mean (41.3 vs 41.8) and median (44 (37–47) vs 44 (39–47)) ages. Reasons cited for amenorrhea included “They stopped naturally” (44.3% of women with CKD vs 48.3% of women without CKD), “Surgery to remove ovaries or uterus” (26.0% CKD vs 38.9% without CKD), and “Other” (29.6% CKD vs 10.5% without CKD). A history of hysterectomy was reported by 7.1% of women with CKD and 6.1% of women without CKD.

Table 2 compares the prevalence odds ratios for self-reported infertility, cessation of menses, and hysterectomy in women with vs. without CKD. Compared to women without CKD, those with CKD did not have a significantly increased odds of infertility (adjusted OR 1.02, 95% CI 0.42–2.49). In a crude comparison, women with CKD had twice the odds of experiencing cessation of menses (OR 2.15, 95% CI 1.15–4.0) but this was attenuated and no longer significant after adjustment for age and BMI (OR 1.25, 95% CI 0.52–3.04). The odds of hysterectomy were not statistically different between women with vs. without CKD (OR 1.17, 95% CI 0.61–2.25) and an adjusted analysis was not performed due to the low number of events. In the sensitivity analyses, the prevalence odds ratios were higher for infertility, cessation of menses, and hysterectomy in women with CKD but the estimates were not substantially different from the base analysis and were not statistically significant (Table 2).

Table 2

Multivariable Adjusted Association Between CKD and Self-reported Infertility, Cessation of Menses, and Hysterectomy Among Reproductive Age Women in the HCHS/SOL

Primary analyses							
Characteristic	n	Infertility		Cessation of Menses		Hysterectomy	
		Unadjusted OR (95% CI)	Adjusted <sup>a</sup> OR (95% CI)	Unadjusted OR (95% CI)	Adjusted <sup>b</sup> OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
No CKD	2,469	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
CKD	120	1.20 (0.49– 2.95)	1.02 (0.42– 2.49)	2.15 (1.15– 4.00)	1.25 (0.52– 3.04)	1.17 (0.61– 2.25)	NA
Sensitivity analyses <sup>c</sup>							
Characteristic	n	Infertility		Cessation of Menses		Hysterectomy	
		Unadjusted OR (95% CI)	Adjusted <sup>a</sup> OR (95% CI)	Unadjusted OR (95% CI)	Adjusted <sup>b</sup> OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
No CKD	2,493	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
CKD	96	1.41 (0.54– 3.69)	1.19 (0.46– 3.10)	2.66 (1.36– 5.20)	1.74 (0.66– 4.61)	1.35 (0.66– 2.77)	NA
Abbreviations: CKD, chronic kidney disease; HCHS/SOL, Hispanic Community Health Study, Study of Latinos; OR, odds ratio; CI, confidence interval; Ref, referent; NA, not applicable.							

Adjusted OR for hysterectomy not performed due to a low number of events

<sup>a</sup> Adjusted for BMI

<sup>b</sup> Adjusted for age and BMI

<sup>c</sup> In the sensitivity analysis, CKD was defined as either a low eGFR (< 60 ml/min per 1.73 m<sup>2</sup>) or a urine albumin to creatinine ratio of > 30 mg/g on spot urine samples at both visits

## CKD and pregnancy loss

At the second visit, 92.9% (n = 112) of women with CKD and 85.4% (n = 2165) of women without CKD reported a history of pregnancy (Fig. 1). A total of 45.9% of women (42.3% of women with CKD and 46.1% of women without CKD) reported a history of nonviable loss. As shown in Table 3, the presence of CKD was not associated with an increased risk of a nonviable pregnancy loss (adjusted OR 0.89, 95% CI 0.53–1.48). The risk appeared to increase when assessing only those women who reported pregnancy occurring after baseline visit (adjusted OR 2.11, 95% CI 0.63–7.02) though this was imprecise and not statistically significant. A sensitivity analysis using the restricted CKD definition showed similar results (Table 3).

Table 3

Association Between CKD and Nonviable Pregnancy Loss Among Reproductive Age Women in the HCHS/SOL

Primary analyses				
	Nonviable loss among women with history of pregnancy at any time (n = 2277)		Nonviable loss among women reporting pregnancy after baseline visit (n = 630)	
Characteristic	Unadjusted OR (95% CI)	Adjusted <sup>a</sup> OR (95% CI)	Unadjusted OR (95% CI)	Adjusted <sup>b</sup> OR (95% CI)
No CKD	Ref.	Ref.	Ref.	Ref.
CKD	0.86 (0.52–1.43)	0.89 (0.53–1.48)	1.81 (0.56–5.90)	2.11 (0.63–7.02)
Sensitivity analyses <sup>c</sup>				
	Nonviable loss among women with history of pregnancy at any time (n = 2277)		Nonviable loss among women reporting pregnancy after baseline visit (n = 630)	
Characteristic	Unadjusted OR (95% CI)	Adjusted <sup>a</sup> OR (95% CI)	Unadjusted OR (95% CI)	Adjusted <sup>b</sup> OR (95% CI)
No CKD	Ref.	Ref.	Ref.	Ref.
CKD	0.88 (0.49–1.60)	0.91 (0.50–1.66)	1.66 (0.43–6.36)	1.80 (0.48–6.81)
Abbreviations: CKD, chronic kidney disease; HCHS/SOL, Hispanic Community Health Study, Study of Latinos; OR, odds ratio; CI, confidence interval; Ref, referent.				
<sup>a</sup> Adjusted for BMI				
<sup>b</sup> Adjusted for Diabetes				
<sup>c</sup> In the sensitivity analysis, CKD was defined as either a low GFR (< 60 ml/min per 1.73 m <sup>2</sup> ) or a urine albumin to creatinine ratio of > 30 mg/g on spot urine samples at both visits				

## Discussion

With a focus on mild to moderate CKD in a Hispanic/Latino population, our study builds upon prior literature evaluating the impact of CKD on women's fertility and reproductive health. An altered hypothalamic-pituitary-gonadal axis and uremic toxins are thought to produce a state of functional menopause in women with advanced CKD or requiring dialysis.[20–22] As such, impaired fertility with anovulatory cycles are common, and it is generally accepted that fertility declines in parallel with kidney disease progression. However, it is unclear what threshold of kidney impairment can be attributed to infertility.[3] Taking into account comorbidities such as obesity and diabetes that are also known to be associated with menstrual irregularities and infertility,[23, 24] our study provides support that mild to moderate CKD may not be associated with increased risk.

Previous research has demonstrated that dysfunctional uterine bleeding, menorrhagia, and amenorrhea are common in women with advanced CKD.[3, 25, 26] Given this, we hypothesized that women with CKD may be at higher risk for undergoing hysterectomy compared to those without CKD. Unfortunately, the small number of events here limited statistical power. In a larger population, data from the Women's Health Initiative found no difference in prevalence of hysterectomy in women with CKD vs women without CKD (1.2% vs 2.0%, p = 0.16) though women with CKD more likely to have had menopause before age 45 years (26% vs 23%, p = 0.02).[27]



Spontaneous abortion, or miscarriage, is the most common complication in early pregnancy, and the incidence in clinically recognized pregnancies is between 8–20%. [28, 29] Well-known risk factors include maternal age over 35 years old, previous spontaneous abortion and maternal smoking, though minority women, including Hispanic/Latino women, may also be at higher risk for miscarriage. [16] Our study seemed to suggest this as well, with 45.9% of parous women reporting at least one nonviable loss (pregnancy loss before 24 weeks). The rates of nonviable pregnancy loss in women with CKD are not well described. In those with advanced CKD or requiring dialysis, the blood urea nitrogen level is inversely related to the length of gestation and offspring's birth weight. [30] For those with milder CKD, it is unclear if mechanisms aside from uremic toxins increase risk of early loss. Although women who receive a kidney transplant can often see a rapid return of fertility, reported miscarriage rates range between 15.4–45% in this population. [31–33] In the general population, elevated preconception maternal blood pressure has been found to increase the risk of miscarriage. [8] Though 30.7% of our CKD cohort were considered to have hypertension, it did not emerge as a strong confounder in our final model when assessing risk for nonviable pregnancy loss.

There are several limitations to our study. In our young, reproductive age women from the HCHS/SOL, CKD was mostly defined by an elevated UACR and was present in a small number (4.6% of women included), which ultimately limited the power of our analyses. While the percent of Hispanic/Latino women of reproductive age with CKD is largely unknown, prior literature has estimated CKD to affect 6% of all reproductive age women. [34] To confirm true chronic kidney disease, we were able to utilize measurements from two study visits, approximately 6.2 years apart. However, borderline values in CKD measurements existed when using a strict cutoff estimated GFR of  $< 60$  ml/min per  $1.73$  m<sup>2</sup> and UACR ratio  $> 30$  mg/g. To include mild CKD, we broadened our definition to include those with an estimated GFR  $< 60$  ml/min per  $1.73$  m<sup>2</sup> at one visit and  $< 70$  ml/min per  $1.73$  m<sup>2</sup> at another as we felt this was still a significantly low GFR to constitute CKD in this young population. We also included those with a UACR  $> 300$  mg/g at either visit as this is considered a clinical cutoff for severely increased albuminuria which has been shown to be a risk marker for CKD progression. [35–37] Finally, we included women with a UACR  $> 30$  mg/g at baseline visit while taking an ACE-I or ARB but UACR  $< 30$  mg/g at the second visit, as we felt this discrepancy could be explained by the anti-proteinuric effects of the medications. Sensitivity analyses performed with a stricter definition of CKD as either an estimated GFR  $< 60$  ml/min per  $1.73$  m<sup>2</sup> or UACR  $> 30$  mg/g at both visits ( $n = 96$ ) showed similar odds ratios among women with CKD.

Importantly, the timing of CKD onset was unknown as we only had measurements from the baseline and second study visit. This may help account for why we did not see an increased risk for nonviable pregnancy loss occurring at any time but did see higher odds ratios in women with CKD when examining pregnancies that occurred specifically after baseline visit. Likewise, the specific dates of pregnancy losses were not provided and only reported as either before or after baseline visit. Thus, while pregnancy could have occurred very close to the baseline visit, for some individuals a nonviable pregnancy loss could have occurred many years prior to the baseline visit. We therefore cannot be fully certain that CKD specifically preceded the loss and as such, only prevalence odds ratios could be performed. Data from the Nurses' Health Study II suggests that early pregnancy loss (especially those between 12–19 weeks) may be associated with increased risk for future type 2 diabetes, hypercholesterolemia, and hypertension. [38] As such, it could be hypothesized that pregnancy loss may also contribute to future CKD by way of an increased burden of CKD risk factors.

Finally, the women's health and reproductive outcomes gathered were self-reported and thus subject to recall bias and/or inaccurate reporting. While infertility was assessed in all women by asking whether they had "ever tried to become pregnant for greater than one year without success", it is currently recognized that for women older 35 years

old, this interval should be shortened to six months.[39] Cessation of menses was assessed by asking whether natural periods had ended but this was not confirmed with biochemical evidence and does not include women who may be menstruating but having anovulatory cycles, a condition that is common in CKD.

## Conclusion

The presence of mild to moderate CKD by our definition did not confer a significant risk of infertility, cessation of menses, or hysterectomy in this Hispanic/Latino cohort. Among women who experienced pregnancy after the baseline study visit, those with CKD had higher adjusted point estimates for nonviable pregnancy loss though this failed to reach statistical significance. Overall, knowledge of pre-pregnancy kidney function and its comorbidities may aid in reproductive counseling and allow for medical optimization before attempting to conceive. Likewise, evaluating for underlying CKD in Hispanic/Latino women who experience nonviable pregnancy loss may also be prudent. Larger prospective studies of women in all stages of CKD attempting to conceive are warranted.

## Abbreviations

HCHS/SOL- Hispanic Community Health Study/Study of Latinos; CKD- chronic kidney disease; ESKD- end-stage kidney disease; U.S.- United States; BMI- body mass index; UACR- urine albumin to creatinine ratio; eGFR- estimated glomerular filtration rate; ACE-I- angiotensin converting enzyme-inhibitor; ARB- angiotensin receptor blocker

## Declarations

Ethics approval and consent to participate: The HCHS/SOL study adheres to the Declaration of Helsinki and was approved by the institutional review boards at each field center where all participants gave written consent at each study visit. This secondary data analysis was reviewed by the University of North Carolina Office of Human Research Ethics and deemed non-human subjects research due to the de-identification of data.

Consent for publication: Not applicable.

Availability of data and materials: *The data that support the findings of this study are available from HCHS/SOL by permission.* Data are available from the authors upon reasonable request and with permission of HCHS/SOL.

Competing interests: The authors declare that they have no competing interests

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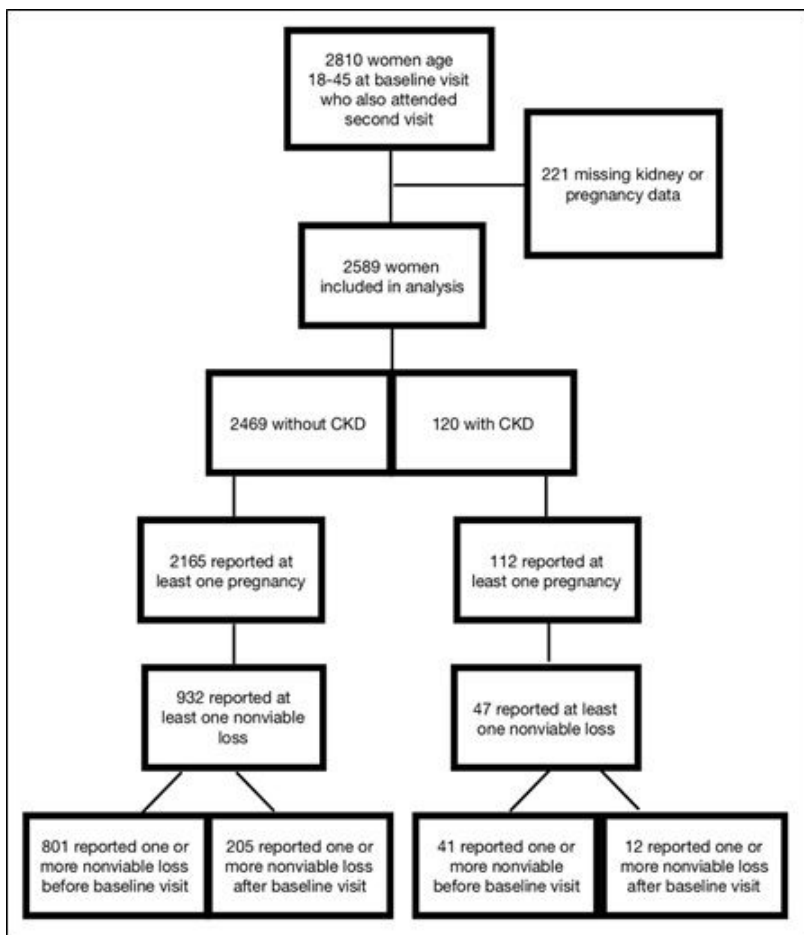
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## Figures



**Figure 1**

Participant Inclusion and Pregnancies Reported by Reproductive Age Women With and Without CKD at the HCHS/SOL Second Study Visit (2014-2017) . Abbreviations: CKD, chronic kidney disease; HCHS/SOL, Hispanic Community Health Study, Study of Latinos

## Supplementary Files

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