Perinatal morbidity and mortality of children born to mothers with chronic kidney disease

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Abstract

Introduction: Chronic kidney disease (CKD) associated with pregnancy increases the risk of maternal and fetal complications. **Objective:** To determine perinatal morbidity and mortality of children born to mothers with mild and moderate CKD during pregnancy. **Methods:** Retrospective study of medical records of women with mild and moderate CKD during pregnancy cared for at La Raza National Medical Center between 2010 and 2016. **Results:** There were 142 patients, 99 (69.72%) with mild CKD and 43 (30.28%) with moderate CKD; 79 neonates (55.63%) reached full term, 28 (19.71%) had growth restriction; 44 (30.98%), low birth weight and 54 (38.02%) were admitted to the neonatal intensive care unit (NICU); and four women (4.04%) had an abortion; in four (2.81%), their children had intrauterine death, and in 10 (7.04%), neonatal death. High blood pressure (odds ratio [OR] = 6.93) and hemoglobin < 11 g/dL (OR = 2.48) were risk factors for prematurity. **Conclusion:** A relationship was found between anemia and blood pressure levels and risk for prematurity, low Apgar, and NICU admission.

KEY WORDS: Mild kidney disease. Moderate kidney disease. Pregnancy. Perinatal mortality.

Morbilidad y mortalidad perinatal de hijos de mujeres con enfermedad renal crónica

Resumen

Introducción: La enfermedad renal (ER) crónica asociada al embarazo incrementa el riesgo de complicaciones maternas y fetales. **Objetivo:** Determinar la morbilidad y mortalidad perinatal del hijo de madre con enfermedad renal leve y moderada del embarazo. **Métodos:** Estudio retrospectivo de expedientes de mujeres con ER leve y moderada del embarazo atendidas en el Centro Médico Nacional La Raza entre 2010 y 2016. **Resultados:** Se trató de 142 pacientes, 99 (69.72 %) con ER leve y 43 (30.28 %) con ER moderada; 79 (55.63 %) neonatos llegaron a término, 28 (19.71 %) presentaron restricción de crecimiento; 44 (30.98 %), peso bajo al nacimiento y 54 (38.02 %) ingresaron a la unidad de cuidados intensivos neonatales; cuatro (4.04 %) mujeres presentaron aborto, en cuatro (2.81 %) sus hijos presentaron muerte intrauterina y en 10 (7.04 %), muerte neonatal. La presión arterial alta (RM = 6.93) y la hemoglobina < 11g/dL (RM = 2.48) constituyeron factores de riesgo para prematuridad. **Conclusión:** Se encontró relación entre la anemia y las cifras de tensión arterial como riesgo para prematuridad, Apgar bajo e ingreso a unidad de cuidados intensivos neonatales.

PALABRAS CLAVE: Enfermedad renal leve. Enfermedad renal moderada. Embarazo. Mortalidad perinatal.

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Introduction

The incidence of chronic kidney disease (KD) associated with pregnancy is approximately 0.03 to 0.12% according to registries in the North American population and 0.33% according to a Mexican study^{1,2}. This association increases the risk of maternal and fetal complications. The most common fetal complications are intrauterine growth restriction (IUGR), low birth weight, longer hospital stay and perinatal death¹⁻³.

Serum creatinine remains the gold standard for evaluating kidney function in pregnant women. The Davison-Lindheimer classification in pregnancy divides pregnant women with KD into three categories according to serum creatinine levels:

- With mild KD, creatinine < 1.4 mg/mL.
- With moderate KD, creatinine between 1.4 and 2.8 mg/dL.
- With severe KD, creatinine > 2.8 mg/dL^{4,5}.

The effects of KD on pregnancy include an increase in adverse fetal outcomes, which is correlated with KD severity before pregnancy^{6,7}. In a study of 38 pregnant women with KD, Bar et al. described prematurity in 22% and IUGR in 13%^{8,9}. In 67 patients with glomerular filtration < 60 mL/minute/1.73 m², Jones and Hayslett found prematurity and IUGR in 59%, as well as fetal survival in 93%¹⁰⁻¹². In a meta-analysis, Nevis et al. identified poorer fetal outcomes in women with KD with regard to those without this condition, such as premature birth, short length for gestational age and low birth weight, with odds ratios (ORs) of 1.8, 2.67 and 4.85, respectively^{13,14}. Fetal and neonatal survival is lower when blood pressure levels are uncontrolled, with and without proteinuria (> 500 mg/day), as reported by Lindheimer and Katz¹⁵⁻²³.

The purpose of the present study was to determine perinatal morbidity and mortality of newborns of women with mild and moderate KD of pregnancy.

Methods

A retrospective cohort of 142 neonates born to women with mild and moderate chronic KD, cared for between January 1, 2010, and December 31, 2016, at La Raza National Medical Center was analyzed; based on serum creatinine, they were stratified according to Davison-Lindheimer classification (Appendix 1).

Demographic and clinical data were obtained from medical records. Of the women, the week of pregnancy diagnosis, comorbidities and KD evolution time

were captured. Newborns had decreased intrauterine growth (below 3rd percentile), low birth weight (< 2500 g), stillbirth and admission to the neonatal intensive care unit (NICU) recorded.

Data are expressed as frequencies, medians, and interquartile ranges or means $\pm$ standard deviations according to the variables' characteristics. The differences between groups were analyzed with the chi-square test or Student's t-test, as appropriate. To establish risks, binary and multiple logistic regression calculation was performed. The Statistical Package for the Social Sciences program, version 25, was used.

Results

Between January 2010 and December 2016, 142 neonates born to women with mild and moderate chronic KD of pregnancy were registered. The group of neonates born to women with mild KD was made up of 99 subjects (69.72%) and that of neonates born to women with moderate KD, of 43 (30.28%).

Pregnant women baseline characteristics that influenced on fetal outcomes are described in table 1. Mean age was 29.2 years, with a minimum of 18 and a maximum of 44; the proportion of patients with comorbidities was 57.57% in the group with mild KD and 55.81% in the group with moderate KD. Maternal and fetal indications for pregnancy resolution are shown in table 2.

The main indication for pregnancy termination was pre-eclampsia with data consistent with severity, the second was chronic KD and the third differed in both groups: in patients with mild KD, it was labor active phase (n = 8, 8.08%), and in the group with moderate KD, renal function deterioration (n = 7, 16.27%). Cesarean section was the most used modality for terminating pregnancy.

Gestational age was calculated using the Capurro method: median of 35.31 weeks in the group of women with mild KD and 34.39 weeks in the group with moderate KD. Average weight of the newborns of women with mild KD was 2423 g and 2140 g in the children of women with moderate KD. Weight was adjusted by percentile according to gestational age, given the direct relationship between both characteristics (Appendix 2).

Full-term was reached in 55.63% of pregnancies, 35.91% of the children were premature (from 28.1 to 36.6 weeks of gestation) and 4.92% (< 28.1 weeks), extremely premature. IUGR occurred in 19.71%, low weight for gestational age in 30.88%, Apgar indicative of moderate depression in 3.52%, Apgar indicative of

Table 1. Baseline characteristics of women during pregnancy

Characteristics	Mild KD (n = 99)		Moderate KD (n = 43)		p*
	Median	Min, Max	Median	Min, Max	
Age (years)	29.45	18, 44	28.65	18, 40	0.664
Gestations	2.07	1, 5	1.93	1, 4	0.513
Deliveries	0.33	0, 2	0.37	0, 2	0.682
Abortions	0.38	0, 2	0.34	0, 2	0.945
Cesarean sections	1.32	0, 3	1.11	0, 3	0.164
Hemoglobin (g/dL)	11.97	9.3, 16.8	11.40	9, 16.5	0.450
Albumin (mg/dL)	3.14	1.8, 6.6	3.01	1.4, 4.7	0.380
Creatinine (mg/dL)	0.95	0.5, 1.5	1.84	1.4, 2.7	< 0.001
Urea (mg/dL)	29.75	11, 107.9	55.95	20.8, 126	< 0.001
Cr clearance (mL/minute)	86.98	24, 188.7	48.53	13.87, 188	< 0.001
Cr clearance (CKD-EPI)	83.34	45.3, 138.3	39.04	21.3, 54.7	< 0.001
Proteinuria (g)	0.571	0, 6.6	1.97	0.025, 9.62	0.086
	n	%	n	%	
No proteinuria (< 300 mg)	79	79.79	24	55.81	
Proteinuria 300 mg to 1 g	6	6.06	8	18.60	
Proteinuria ≥ 1 g	14	14.14	11	25.58	
Comorbidities	57	57.57	24	55.81	
No diabetes mellitus	92	92.92	38	88.37	
Gestational diabetes	1	1.01	0		
DM1	5	5.05	5	11.62	
DM2	1	1.01	0		
No HBP	55	55.55	22	51.16	
Gestational hypertension	28	28.28	5	11.62	
HBP	16	16.16	16	37.20	
Systemic lupus erythematosus	5	5.05	3	6.97	
KD diagnosed < 20 WOG	23	23.23	11	25.58	
KD diagnosed > 20 WOG	47	47.47	19	44.18	

*Mann-Whitney's U-test.

KD = kidney disease; Cr = creatinine; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration (mL/minute/1.73 m²); DM = diabetes mellitus; HBP = high blood pressure; WOG = weeks of gestation.

severe depression in 6.33%, and admission to the NICU in 38.02% (Table 3).

Newborns overall survival was 86.04% in the group of children of mothers with moderate KD, and 86.86% in the children of mothers with mild KD, with a total of four abortions (4.04%) in the group of mild KD and one (2.32%) in the group with moderate KD. Multivariate logistic regressions were performed for each one of the independent variables regarding perinatal outcome: the presence of anemia (hemoglobin < 11 g/dL) increased 2.92 times the risk of miscarriage (OR = 2.92, 95% confidence interval [CI] =

0.45-18.3, p = 0.22), and the presence of KD increased 1.76 times the risk of abortion (95% CI = 0.19-16.3, p = 0.52) (Table 4).

As for independent variables with statistical significance, uncontrolled blood pressure was observed to increase 93 times the risk of having a premature pregnancy termination (95% CI = 1.43-33.4, p = 0.0092) with regard to ending pregnancy at term, and anemia (hemoglobin < 11 g/dL) increased it 2.48 times (95% CI = 1.21-5.11, p = 0.017); mild and moderate KD showed a trend towards risk for prematurity of 1.88 times (95% CI = 0.90-3.90, p = 0.08), without

Table 2. Indications for pregnancy interruption

Indications	Mild KD		Moderate KD		Total	
	n	%	n	%	n	%
Maternal						
Kidney disease	19	19.19	8	18.60	27	19.01
Impaired renal function	2	2.02	7	16.27	9	6.33
Preeclampsia with data consistent with severity	33	33.33	15	34.84	48	33.80
Active phase labor	8	8.08	2	4.65	10	7.04
Labor failure to progress	3	3.03	0	0	3	2.11
Cephalopelvic disproportion	3	3.03	4	9.30	7	4.92
Short inter-gestational interval	1	1.01	0	0	1	0.70
Twin pregnancy	0	0	1	2.32	1	0.70
Breech presentation	2	2.02	1	2.32	3	2.11
Iterative cesarean section	4	4.04	1	2.32	5	3.52
History of uterine surgery	1	1.01	0	0	1	0.70
Placenta previa	4	4.04	0	0	4	2.81
Oligohydramnios	2	2.02	2	4.65	4	2.81
Fetal						
Abortion	3	3.03	1	2.32	4	2.81
Stillbirth	1	1.01	1	2.32	2	1.40
Low fetal reserve	8	8.08	0	0	8	5.63
Intrauterine growth restriction	5	5.05	0	0	5	3.52

Table 3. Pregnancy termination route and perinatal outcomes

Termination route	Mild KD		Moderate KD		Total	
	n	%	n	%	n	%
Cesarean section	82	82.82	37	86.04	119	83.80
Delivery	13	13.13	6	13.95	19	13.38
Curettage	4	4.04	0	0	4	2.81
Total	99	100	43	100	142	100
Perinatal outcomes	Median	Max-Min	Median	Max-Min	p	
Weight	2423.59	250-4000	2140.81	300-3350	0.177*	
Weeks of gestation	35.31	10-42	34.39	21-40	0.023*	
5-min Apgar	8.6	5-10	8.6	5-9		
Hospital LOS, days	9.12	0-131	14.88	0-83	0.681*	
NICU LOS, days	3.5	0-131	2	0-27	0.91*	

KD = kidney disease; LOS = length of stay; NICU = neonatal intensive care unit.

*Mann-Whitney's U-test.

statistical significance, and proteinuria, 1.4 times (95% CI = 0.66-2.95, $p = 0.37$).

Anemia was statistically significant (OR = 7.78, 95% CI = 1.54-39.16, $p = 0.008$) in showing a decrease in the Apgar score at five minutes, and KD was related 2.99 times to the risk of Apgar indicative of moderate to severe depression (95% CI = 0.76-11.75, $p = 0.130$).

Blood pressure lack of control increased 3.32 times the risk of IUGR (95% CI = 0.96-11.40, $p = 0.060$).

Elevated blood pressure levels increased 4.44 times the risk of NICU admission.

Discussion

Of the patients with a diagnosis of KD and pregnancy, 99 (69.72%) were assigned to the mild KD group, with 99 (69.72%), whereas 43 (30.28%) were included in the moderate KD group, similar to that reported in the

Table 4. Study variables multivariate analysis with pregnancy outcome in patients with chronic KD

Variables	Abortions n (%)	Births n (%)	OR	95% CI	p*	Premature n (%)	Full term n (%)	OR	95% CI	p*
Chronic kidney disease										
Mild	4 (4.04)	95 (95.96)	1.76	0.19-16.3	0.52	23 (53.5)	20 (46.5)	1.88	0.90-3.9	0.0864**
Moderate	1 (2.33)	42 (97.67)				36 (37.9)	59 (62.1)			
Proteinuria										
Proteinuria	0 (0)	39 (100)	—	—	—	19 (48.7)	20 (51.3)	1.4	0.66-2.95	0.374**
No proteinuria	5 (4.85)	98 (95.15)				40 (40.4)	59 (59.6)			
Blood pressure figures										
Normal	4 (3.08)	126 (96.92)	0.34	0.04-3.4	0.361	9 (81.8)	2 (18.2)	6.93	1.43-33.4	0.0092**
Elevated	1 (8.33)	11 (91.67)				50 (39.4)	77 (60.6)			
Anemia										
Anemia	3 (6.12)	46 (93.88)	2.92	0.45-18.38	0.22	27 (57.4)	20 (42.6)	2.48	1.21-5.11	0.017**
No anemia	2 (2.15)	91 (97.85)				32 (35.2)	59 (64.8)			
	Mod. and sev. Depression n (%)	No depression n (%)	OR	95% CI	p*	IUGR n (%)	No IUGR n (%)	OR	95% CI	p*
Chronic kidney disease										
Mild	5 (11.6)	38 (88.4)	2.99	0.76-11.75	0.13	5 (11.6)	38 (88.4)	0.43	0.15-1.23	0.11
Moderate	4 (4.2)	91 (95.8)				23 (23.2)	76 (76.8)			
Proteinuria										
Proteinuria	2 (5.1)	37 (94.9)	0.71	0.14-3.57	1	10 (25.6)	29 (74.4)	1.62	0.67-3.92	0.27**
No proteinuria	7 (7.1)	92 (92.9)				18 (17.5)	85 (82.5)			
Blood pressure figures										
Normal	0 (0)	11 (100)	—	—	—	5 (41.7)	7 (58.3)	3.32	0.96-11.40	0.06
Elevated	9 (7.1)	118 (92.9)				23 (17.7)	107 (82.3)			
Anemia										
Anemia	7 (14.9)	40 (85.1)	7.78	1.54-39.16	0.008	9 (18.4)	40 (81.6)	0.87	0.36-2.11	0.76
No anemia	2 (2.2)	89 (97.8)				19 (20.4)	74 (79.6)			
	Low birth weight n (%)	Adequate weight n (%)	OR	95% CI	p*	NICU admission n (%)	No NICU admission n (%)	OR	95% CI	p*
Chronic kidney disease										
Mild	12 (27.9)	31 (72.1)	1.234	0.56-2.71	0.6**	6 (14)	37 (86)	0.78	0.28-2.14	0.63
Moderate	32 (32.3)	67 (67.7)				17 (17.2)	82 (82.8)			
Proteinuria										
Proteinuria	15 (38.5)	24 (61.5)	1.595	0.73-3.46	0.23**	7 (17.9)	32 (82.1)	1.18	0.44-3.15	0.72
No proteinuria	29 (28.2)	74 (71.8)				16 (15.5)	87 (84.5)			
Blood pressure figures										
Normal	5 (41.7)	7 (58.3)	1.66	0.49-5.57	0.4	5 (41.7)	7 (58.3)	4.44	1.27-15.52	0.012
Elevated	39 (30)	91 (70)				18 (13.8)	112 (86.2)			
Anemia										
Anemia	16 (32.7)	33 (67.3)	1.12	0.53-2.36	0.75**	9 (18.4)	40 (81.6)	1.26	0.50-3.1	0.61
No anemia	28 (30.1)	65 (69.9)				14 (15.1)	79 (84.9)			

*Fisher's exact test; **Chi-square test.

OR = odds ratio; CI = confidence interval; NICU = neonatal intensive care unit; IUGR = intrauterine growth restriction.

literature, where the largest proportion of patients is referred to have mild KD during pregnancy.

Birth weight recorded in the children of mothers with mild KD was 2423 g (250-4000 g), whereas that of the

children of mothers with moderate KD was 2140 g (300-3350 g), with a difference of 283 g between both groups' median weight, which was not statistically significant with a p-value of 0.177 using

Mann-Whitney's U-test. In the group of women with mild KD, there were 63.63% of newborns with adequate weight for gestational age, 32.32% with low weight for gestational age and 1.01% with high weight for gestational age. In the group of women with moderate KD, 72.09% of newborns were recorded to have adequate weight for gestational age and 27.90% had low weight.

In both groups, 19.71% of IUGR was recorded; in the group with mild KD it was 23.23%, and in the group with moderate KD it was 11.62%, a proportion slightly higher than that reported by Trevisan et al., who indicated 13%, and lower to that reported by Jones and Hayslett, who referred 37% of IUGR, and by Cunningham, who reported 35%.

Gestational age difference at birth was statistically significant between both groups: in women with mild KD, the median was 35.31 weeks, while in women with moderate KD, it was 34.39 weeks, with a p-value of 0.023. In women with mild KD, 59.59% of full-term pregnancies were identified; there were 32.32% of premature newborns of between 28.1 and 36.6 weeks of gestation, and 4.04% were extremely premature. In the group with moderate KD, there were 46.51% of full-term pregnancies, 44.18% of premature newborns of between 28.1 and 36.6 weeks of gestation, and 9.30% were extremely premature. In both groups, 55.63% of full-term pregnancies and 44.37% of premature deliveries were found. In general, preterm neonates were fewer than those reported by Trevisan et al., who indicate 60% of premature newborns, while Jones and Hayslett report 59%. However, they were more than those reported by Cunningham (30%).

Differences in the days of hospital length of stay (LOS) and days of NICU LOS were not statistically significant between both groups, with a p-value of 0.681 for the days of hospital LOS and of 0.910 for the days of NICU LOS. In the group with moderate KD, 86.04% of newborns were admitted to the NICU, while in the group with mild KD only 17.17% were admitted.

Five-minute Apgar score was 7 to 10 (no depression) in 90.90% of the children of mothers with mild KD and in 88.37% of the children of mothers with moderate KD; 4.04% of the children of mothers with mild KD showed moderate depression (4 to 6 Apgar score) in comparison with 2.32% of the children of mothers with moderate KD. Severe depression (Apgar ≤ 3) was recorded in 5.05% of the children of mothers with mild KD and in 9.30% of the children of mothers with moderate KD.

Overall survival of the neonates was 86.61% for both groups, 86.04% in the group of children of mothers with moderate KD, and 86.86% in the children of mothers with mild RD, which is slightly lower than the 93% rate reported by Jones and Hayslett and slightly higher than the 82% rate referred by Jungers et al. after excluding first trimester abortions (which were taken into account in our study). In the group of women with mild KD, abortion was recorded in 4.04%, and regarding their children, intrauterine death in 1.01%, early neonatal death in 6.06% and late neonatal death in 2.02%; in the group of women with moderate KD, abortion was recorded in 2.32%, intrauterine death in 6.97%, early neonatal death in 2.32% and late neonatal death in 2.32%.

Blood pressure figures lack of control ($p = 0.0092$) and hemoglobin < 11 g/dL ($p = 0.017$) showed a statistically significant relationship with premature birth. Apgar < 3 , which indicates moderate and severe depression, was statistically significant with hemoglobin levels < 11 g/dL ($p = 0.008$).

NICU admission had a statistically significant relationship with uncontrolled blood pressure figures ($p = 0.012$). Low birth weight, IUGR, abortion, intrauterine death and neonatal death showed no statistically significant relationships with the degree of KD (mild and moderate), proteinuria, hemoglobin levels and blood pressure figures. Unlike the findings reported by Zhang et al., who refer that uncontrolled hypertension and proteinuria worsen fetal outcomes, in this study, a statistically significant relationship was only found between uncontrolled blood pressure levels and the birth of premature children and NICU admission. Proteinuria had no statistically significant relationship with perinatal morbidity and mortality results; however, taking these results with caution is advised, since they differ from those reported in the literature and could be caused by inadequate 24-hour urine collection.

Hemoglobin levels < 11 g/dL had a statistically significant relationship with Apgar scores < 3 and with the birth of premature children. This has not been reported in the literature, since, in most studies, maternal hemoglobin is evaluated in patients with severe KD during pregnancy and it is not reported in patients with mild and moderate KD.

Conclusions

Average age in both groups was 29 years; the KD cause was unknown in 48.48% of women with mild and

in 76.74% with moderate disease; the main indication for pregnancy termination was preeclampsia with data consistent with severity, and the second, chronic KD. Average gestational age at birth was 35.31 and 34.39 weeks and birth weight was 2423 and 2140 g in the children of women with mild and moderate KD, respectively. Unlike observations reported in the literature, no statistically significant relationship was found between proteinuria and perinatal adverse outcomes; however, anemia and elevated blood pressure figures were statistically significantly associated with prematurity, low Apgar score and NICU admission.

Based on our findings, we believe that prospective studies should be conducted, and follow-up of the mother and the child before, during and after pregnancy should be carried out in a protocol-based and multidisciplinary manner in order for perinatal results to be improved.

Conflict of interests

The authors declare that they have no conflicts of interest.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

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Appendix 1. *Classification of kidney disease during pregnancy.*

Davison-Lindheimer classification	
Mild kidney disease	Serum creatinine < 1.4 mg/dL
Moderate kidney disease	Serum creatinine > 1.4 mg/dL - < 2.8 mg/dL
Severe kidney disease	Serum creatinine > 2.8 mg/dL

Appendix 2. *Jurado-García graph. Correlation of birth weight with gestational age.*