ORIGINAL ARTICLE

Use of Renal Replacement Therapy in Pregnant Women with Acute Kidney Injury or Chronic Kidney Disease: A Systematic Review

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ABSTRACT

Objectives. Acute Kidney Injury (AKI) during pregnancy is a complication that poses a serious risk of life for the mother and the fetus. In most cases, the treatment considered in the first instance is pregnancy interruption with subsequent conventional treatment of AKI. The aim of this review is to describe the risks and benefits of using renal replacement therapy [peritoneal dialysis (PD) and hemodialysis (HD)] in pregnant patients with AKI.

Methods. A systematic review of pregnant women with AKI/CKD on RRT (pointing out the results of maternal and neonatal morbidity and mortality) in the last three decades was done between January and March 2021 using the databases Pubmed, LILACS, Cochrane, Tripdatabase, AJKD, and Elsevier. Articles in Spanish, English, and French languages were included. A summary of cases of pregnant women on RRT with women and fetus survival percentages was shown in a table.

Results. Making a summary of all the included patients, it resulted in 1673 women, 1208 in HD and 170 in PD with 15 maternal deaths and survival percentages for the fetus of 74% in HD and 40% in PD.

Conclusion. The RRT in pregnant women with AKI/CKD offers a high survival rate for the women and fetus.

Keywords: hemodialysis, kidney injury, peritoneal dialysis, pregnancy, renal replacement therapy

INTRODUCTION

In normal conditions, during pregnancy, the glomerular filtration rate increases 50% with subsequent decrease in serum creatinine, urea, and uric acid values. Also, osmolality and serum sodium levels are decreased as a result of a lower threshold for thirst and antidiuretic hormone secretion. These changes lead to blood pressure decrement of about 10 mmHg by the second trimester despite a gain in intravascular volume of 30% to 50%.[1]

Acute Kidney Injury (AKI) during pregnancy is a potentially devastating complication, capable of affecting both the mother and the fetus. It can be related to pre-existing kidney disease, or develop as a new entity during pregnancy. It is likely that, pre-existing chronic kidney disease (CKD) occurs in approximately 4% of parturient women. From these, 43% have a higher risk of developing kidney dysfunction during pregnancy, while 10% of them show a rapid kidney function deterioration.[2,3] The term AKI, allows the early identification of small alterations in renal function, expressed in increased serum creatinine[4], the lack of timely

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intervention leads to patients requiring Renal Replacement Therapy (RRT)[5].

The global Maternal Mortality Rate (MMR) improvement is partially attributed to the AKI classifications used for early diagnosis, in this regard, the classifications of RIFLE (Risk, Injury, Failure, Loss, and End-stage renal failure) and AKIN (Acute Kidney Injury Network) have been developed to determine the diagnosis and prognosis of this condition.[6–8] Of particular concern, the renal failure incidence in pregnant women can reach, depending on the etiology, up to 24%.[9]

Pregnancy-related acute kidney injury (Pr-AKI) defines AKI during pregnancy, childbirth, or the puerperium;[10,11] its incidence has decreased dramatically in recent decades, reaching 1.6 to 6.3 per 10,000 pregnancies[10,12,13]. However, it remains high in developing countries, estimated between 4% and 26% of pregnancies.[10,11,14]

Pr-AKI is a heterogeneous syndrome with a multitude of underlying etiologies, with different prevalence depending on the trimester of pregnancy.[15–18] As in non-pregnant patients, the causes of AKI are divided into: prerenal, renal, and postrenal.[12,13,19] According to Vijayan et al., pregnancy-related causes of AKI are preeclampsia, acute fatty liver of pregnancy (AFLP), HELLP syndrome, and thrombotic microangiopathies such as Thrombotic Thrombocytopenic Purpura (TTP) and atypical Hemolytic Uremic Syndrome (HUS).[20]

Prerenal causes are usually due to hemodynamic alterations such as massive bleeding, miscarriage, amniotic fluid embolism, adrenocortical insufficiency, chorioamnionitis, hyperemesis gravidarum, pyelonephritis and puerperal sepsis,[12–14,16,19,21] Pr-AKI complications include low birth weight, miscarriage, premature delivery and stillbirth.[22]

Pr-AKI causes include preeclampsia/eclampsia, AFLP, and HELLP syndrome.[13,19] Hypertensive disorders (preeclampsia-eclampsia, gestational hypertension, chronic renal hypertension, and pre-existing hypertension with preeclampsia) are the most common complications during pregnancy, childbirth, and puerperium.[23–25] The multiple changes in renal physiology during pregnancy make it difficult to define Pr-AKI.[19,26]

All pregnant patients at risk of AKI should have a detailed medical history with a complete physical examination and laboratory tests for a timely diagnosis.[13,19,20,27] Renal echography, specific laboratory tests, and renal biopsy are reserved when the diagnosis is not clear.[13,20]

The Pr-AKI post-renal causes include hydronephrosis due to uterine compression, injury to the ureters or the bladder during cesarean section, ureteral obstruction by stones or tumor, mechanical changes induced by multiple gestations, polyhydramnios or fibroids, and bladder outlet obstruction.[12,14,16,20]

There is a changing pattern of the Pr-AKI etiology, with a decrease in early pregnancy causes like miscarriage and puerperal sepsis and an increase in causes in late pregnancy due to hypertensive disorders and thrombotic microangiopathies. This change is partially thanks to advances in obstetric care and new maternal risk factors.[11,18,20,28]

Pregnancy complicated by AKI is a therapeutic challenge.[11,20,29] Prevention is through volume replacement, management of high-risk obstetric conditions, and avoiding nephrotoxic antibiotics.[22] In most cases, the AKI during pregnancy responds to support measures; if despite these interventions, kidney injury progresses, signs of uremia develop, or the approach is unsuccessful, RRT may be necessary. Kidney failure can progress to the point of requiring dialysis, in this line, both peritoneal dialysis (PD) and hemodialysis (HD) have been used successfully to treat kidney failure during pregnancy.[15] RRT indications for pregnancy are the same for general population: a) serum potassium with a value of 6.5 meq/L resistant to medical treatment, b) circulatory congestion, secondary to fluid overload that does not respond to diuretic therapy or in those who develop progressive volume overload despite fluid restriction, c) severe uremic symptoms (pericarditis, neuropathy, or encephalopathy), d) Blood Urea Nitrogen greater than 120 mg/dL or a daily increase of 30 mg/dL in patients with sepsis or tubular necrosis, and e) metabolic acidosis, without improvement.[18,20]

Other cases such as septic miscarriages or thrombotic microangiopathies can be life-threatening and require urgent dialysis.[11,13,19] RRT should be considered in patients with the development of anuria or azotemia.[11] The aim of this review is to describe the risks and benefits of using RRT (PD and HD) in pregnant patients with AKI.

METHODS

A systematic review of articles in Spanish, English, and French languages, was performed between January and March 2021, using the databases Pubmed, LILACS, Cochrane, Tripdatabase, AJKD, and Elsevier in pregnant women with CKD and ARD on RRT from the year 1990 to 2020, pointing out the maternal and neonatal morbidity and mortality results before, during, and after delivery.

The search terms or variations of the following terms (MeSH, DeCS) were used in databases:

1. "Acute Renal Failure" AND "Renal Replacement Therapy" AND "Pregnancy"
2. "Acute Kidney Injury" AND "Renal Replacement Therapy" AND "Pregnancy"
3. "Acute Renal Failure" AND "Dialysis" AND "Pregnancy"
4. "Acute Kidney Injury" AND "Dialysis" AND "Pregnancy"
5. "Acute Renal Failure" AND "Hemodialysis" AND "Pregnancy"
6. "Acute Kidney Injury" AND "Hemodialysis" AND "Pregnancy"
7. "Embarazo" y "Falla renal aguda" y "Diálisis"
8. "Embarazo" y "Falla renal aguda" y "Hemodiálisis"
9. "Embarazo" y "Falla renal aguda" y "Terapia de Sustitución Renal"

These terms were used either across the full articles or as a topic depending on the search options in the databases. A search of the literature was carried out independently by each of the authors using the exclusion criteria to add or not an article to the database. Inclusion criteria were: use of RRT during or before pregnancy, women of all age groups were included, use of HD or PD, women with CKD or development of AKI during pregnancy, and databases pointing out the results of maternal and neonatal morbidity and mortality. Exclusion criteria were: non-pregnant women, women without documentation of the use of RRT, women without development of CKD or AKI, and databases that did not report complications during the use of RRT, and those studies related to animals (Figure 1).

The outcomes of interest were number of pregnancies, cases on HD, cases on PD, maternal mortality, percentage of live births, and main complication. No more variables were sought.

After all the authors searched for articles independently, they established online work sessions to compare and analyze the information gathered. The collaborators of this project worked on a folder in a Drive to upload and cross-check the information. Statistical analysis was performed using Excel. If the information about the variables of interest was not found in an article, the annotation "NR: not reported" was placed in the table.

The protocol was approved by the Ethics in Research Committee of the Hospital Materno-Perinatal "Mónica Pretelini Sáenz" (2021-08-751), Health Institute of the State of Mexico (ISEM), Toluca, Mexico, and informed consent was waived as the medical data was obtained from historical files. This protocol was registered in the State Health Research Registration System (seris web).

RESULTS

A total of 58 articles were identified from the literature search. Only 18 articles were included, five from the USA, three from Brazil, and one each from Australia, Canada/UK, Chile, China-Taiwan, France, Japan, Mexico, Saudi Arabia, South Korea, and Tunisia.

Making a summary of all the included patients, it resulted in 1673 women, 1208 in HD and 170 in PD with 15 maternal deaths and survival percentages for the fetus of 74% in HD and 40% in PD (Table 1).

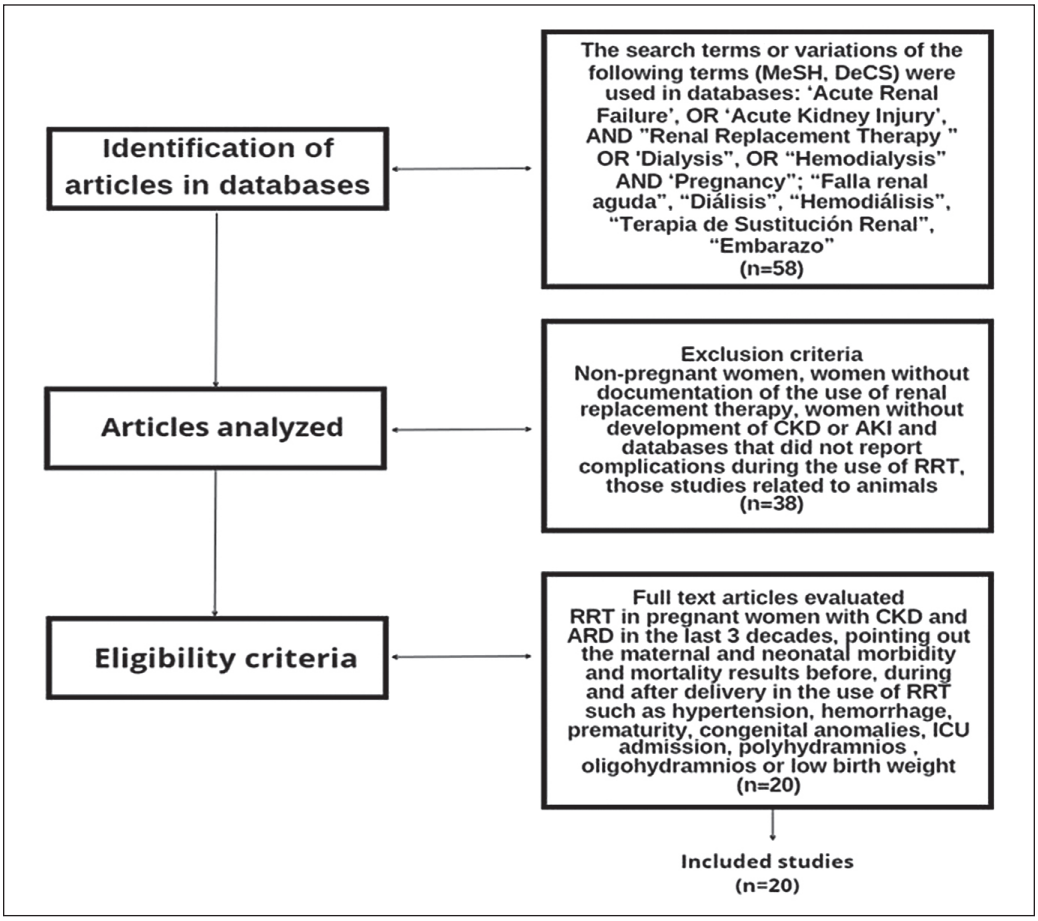

Figure 1. Flowchart used in the selection of studies.

Table 1. Main Studies about Maternal-fetal Morbidity and Mortality, and Complications on Pregnant Patients with CKD/AKI

Study	Number of pregnancies	HD	PD	Maternal deaths	Live births (%)	Complications	Risk of Bias
Hou (1994)[30]	60 patients with CKD Information on the mode of dialysis was available in 33 pregnancies.	26	7	NR	37%	• Two episodes of malignant hypertension. • Two bleeding complications. • One postpartum hemorrhage, an intraperitoneal hemorrhage. • One DIC. • Prematurity in all live births except one. • 20% with low weight for GA.	This study has bias in selection of the reported results because the information was collected through questionnaires with a change in fetal survival since 1990.
Okundaye et al. (1998)[31]	344 pregnant women with CKD	305	18	2	49.5%	• Five women were admitted to the ICU for hypertension control. • Five episodes of peritonitis in patients on PD. • 11 babies were born with congenital anomalies. • Low weight for GA 28%.	This study has selection bias because questionnaires were sent to the 2,299 dialysis centers.
Romão Jr et al. (1998)[32]	17 pregnant women with CKD	14	3	NR	70.6% general 78.6% with HD and 33.3% with PD	• Polyhydramnios in seven cases (5 HD and 2 in PD). • Oligohydramnios in one patient (HD). • Fetal distress in 10 cases (9 in HD and 1 in PD). • Hypertension in eight patients (7 on HD and 1 on PD). • The mean GA was 32.3 ± 2.6 weeks. • The NB mean weight was 1400.7 ± 579.1 g. • No congenital fetal abnormalities were observed.	This study has a bias in study design because of few cases (17 pregnant women).
Hou S & Firanek C. (1998)[33]	344 pregnant women with CKD	229	115	2	23% of pregnancies with PD 75-80% of pregnancies with HD	• 25% of pregnancies end in miscarriage, stillbirth, or neonatal death. • 80% premature birth. • 36% of NB weighted less than 1500 g. • There is very little follow-up of its growth. • 80% of women with hypertension.	This study has a bias due to missing outcome data.
Toma et al. (1999)[34]	74 pregnant patients with CKD	74	0	NR	60.8%	• The mean GA was 31.9 ± 4.5 weeks. • Birth before week 37 at 86.7%. • The weight of the NB was 1543.5 ± 671.9 g. • All NBs weighing less than 1000 g (31.1%) died. • Retinopathy of prematurity in 8.9%. • NBs with cerebral palsy 4.4% and cerebral atrophy 4.4%. • Premature uterine contraction in 84.4%. • Polyhydramnios at 53.3%. • Severe hypertension in 42.2%.	This study has selection bias because questionnaires were sent to the 2,299 dialysis centers and 143 renal transplantation units.
Hou (1999)[35]	196 pregnant women with CKD	NR	NR	3	Greater than 70%	• Prematurity 43% to 73%: mean GA of 32.4 weeks. • Intrauterine growth restriction 22% to 57%. • NBs with less than 1500 g 36%. • 80% of pregnant women with a blood pressure higher than 140/90 mmHg.	This study has a bias in study design as this was a narrative review.
Malik et al. (2005)[36]	12 pregnancies in 9 women with CKD	9	0	NR	58%	• 66% women with preeclampsia. • 100% with preterm delivery. • All NBs with low birth weight in the range of 1115-2300 g. • The mean GA was 31.5 weeks. • Polyhydramnios in four pregnancies. • Oligohydramnios in one pregnancy.	Probably this study has a detection bias because from 113 childbearing age women on HD or PD, only nine got pregnant.
Chou et al. (2008)[37]	13 pregnancies in 13 women undergoing chronic dialysis	10	3	NR	70.9% in HD patients 64.2% in patients on PD	• Polyhydramnios in 71% of cases. • Maternal hypertension in 57%. • The mean GA was 30.8 weeks. • The mean weight at birth was 1511 ± 284 g.	Probably this study has a detection bias.
Luders et al. (2010)[38]	52 pregnant patients	52	0	NR	87%	• Mean GA from 32.7 to 3.1 weeks. • 40.4% of pregnancies were complicated by polyhydramnios. • Preeclampsia in 19.2% women. • Hypertension in 67.3% women.	This study has selection bias because it was a retrospective survey.
Shahir et al. (2013)[39]	49 pregnancies in women with CKD	41	8	NR	79%	• Preeclampsia in 19.4%. • 5% developed polyhydramnios. • One NB had a congenital malformation. • 53.4% of NBs were born premature. • 65% of NBs had low birth weight. • 35% had very low birth weight. • The mean weight at birth was 2131 g.	Because it was a very long study, there may be performance bias due to changes in AKI management through time.

Table 1. Main Studies about Maternal-fetal Morbidity and Mortality, and Complications on Pregnant Patients with CKD/AKI *(continued)*

Study	Number of pregnancies	HD	PD	Maternal deaths	Live births (%)	Complications	Risk of Bias
Hildebrand et al. (2015)[40]	188 patients with Pr-AKI	183	5	8	92.7%	• NBs with low birth weight 26.6%. • Small NB for GA 8%. • Preterm pregnancy 32.5%. • Preeclampsia 21.3%. • Thrombotic microangiopathy 13.3%. • Sepsis 18.1%. • Gestational hypertension 3.2%.	This study has selection bias because it was a retrospective population-based cohort study.
Chang et al. (2016)[41]	5 with CKD	4	0	NR	100%	• Need for erythropoietin in pregnant women. • 60% premature delivery. • Mean GA 32.7 ± 4.7 weeks. • Three women experienced preeclampsia. • Two term infants had low birth weight. • Three preterm infants had very low birth weight. • Four had to enter the NICU with 131.0 ± 94.5 days of stay. • Respiratory distress syndrome in all preterm births.	Probably this study has a detection bias because the recruiting period included two years and the cases were few.
Normand et al. (2018)[42]	100 pregnancies in 84 CKD patients	100	0	NR	78%	• Preeclampsia 18.8%. • Polyhydramnios 42.2%. • Induction of labor 74.1% • The mean GA was 33.2 ± 3.9 weeks. • Premature delivery 76.9%. • Low birth weight 44.6%.	This study has selection bias.
Luders et al. (2018)[43]	93 pregnancies in 89 CKD patients	93	0		89.2%	• The mean GA was 35 weeks. • Preeclampsia in 13. • Average weight 1698 g. • 45 were small for GA. • 49 had polyhydramnios.	This study has selection bias because it was a retrospective survey. Four patients had two pregnancies on HD.
Hernández Rivera et al. (2019)[44]	40 pregnancies in 39 women with CKD	39	0	NR	77.4%	• 29 preterm deliveries and one full-term delivery. • 15 women had preeclampsia. • One with eclampsia and one with HELLP syndrome. • Two neonates presented malformations. • Early term at 19. • Extreme preterm at 5. • Hypertensive disorders in 37.5%.	This study has selection bias because it was a retrospective survey. Thirty-nine (39) singleton and one twin pregnancy.
Hoffman, Sibai (2019)[45]	20 pregnancies in 19 CKD patients	20	0	NR	84.22%	• Preeclampsia from 28.6% to 22.2%. • Chorioamnionitis from 28.6% to 22.2%. • Need to enter the ICU 11.1%. • Average birth weight 1322 to 1630 g. • Admission to the NICU 100%.	This study has limited biases. One patient had two pregnancies.
Fiedler et al. (2019)[46]	13 pregnancies in 11 patients with CKD	13	11	NR	82%	• Severe arterial hypertension 54%. • Severe anemia 46%. • Polyhydramnios 31%. • Uterine growth restriction 23%. • Cholestasis 23%. • Severe hypotension associated with HD 15%. • Average GA of 34 weeks. • Average weight 1880 g.	Probably this study has a detection bias because the recruiting period was long with few cases. Two patients had two pregnancies.
Chaker et al. (2020)[47]	25 pregnancies in 19 CKD patients	25	0	NR	56%	• Average GA of 34 weeks. • Average neonatal weight 1970 g. • Hypertension in 37% of pregnant women. • Prematurity 60%. • Uterine growth delay 52%. • Hydramnios at 16%.	This study has selection bias because the initial contact was with a telephone call to the specialized centers. Six patients had two pregnancies.
Total	1673	1208	170	15	74% in HD and 40% in PD		

CKD: Chronic Kidney Disease, DIC: Disseminated intravascular coagulation, GA: gestational age, HD: hemodialysis, ICU: intensive care unit, NB: Newborn, NICU: neonatal intensive care unit, NR: not reported, PD: peritoneal dialysis, Pr-AKI: Pregnancy-related acute kidney injury, RRT: renal replacement therapy.

DISCUSSION

In the general population, patients starting on long-term HD therapy, the mortality rate is increased with advancing age and female gender.[48] CKD patients who experience superimposed AKI have been shown to be at higher risk of long-term sequelae of AKI when compared to those who do not experience AKI.[49]

Pr-AKI is a rare complication with a poor prognosis. Reports from India revealed a decrease of Pr-AKI from 15% to 1.5% in the 2010s, 30% were severe and required dialysis. The records were similar in China, where 80% were in rural areas and 6% required dialysis. A study in Morocco reported 6.6 cases of Pr-AKI per 1000 deliveries, where 16% required dialysis. Paradoxically, Canada and the United States have reported a higher incidence of Pr-AKI.[18,28,29]

A previous publication compiles the information of two studies, one from the National Institute of Perinatology (INPer), Mexico, showing that the prognosis of Pr-AKI treated with dialysis depends on three variables: the underlying cause, severity of kidney failure, and associated complications. Although the MMR was 0%, the fetal mortality was 55.55%. The second study, performed at the Hospital Civil de Guadalajara, Mexico, during 2013-2015 showed that 10 of 27 pregnant patients with stage 3-5 CKD or nephrotic proteinuria had Pr-AKI and required RRT during pregnancy. Most of the women delivered small or very young premature neonates.[14] With this background, it is currently contradictory that in pregnant women with a complication of AKI, the primary therapeutic indication is to interrupt the pregnancy, while the decision to continue the pregnancy is a valid option in women with CKD in RRT.

There is limited standardized data on the time of initiation, duration of therapy, or choice of modality in Pr-AKI; therefore, dialysis prescription needs to be individualized.[12,18,50] The method depends on the hemodynamic state and treatment availability since any dialysis modality can be used during pregnancy. Though there are no randomized trials that show benefits for a specific modality, intermittent HD is the most used technique; however, continuous RRT is necessary for the hemodynamically unstable patient. The advantage of PD over HD is that it causes less intravascular volume fluctuations which could be potentially beneficial for fetal blood flow, but it has the disadvantage of limiting the dialyzed volume due to enlargement of the uterus.[11,18–20]

On pregnant women with AKI receiving RRT, the results of women undergoing HD are usually good. Preeclampsia, third-trimester hematocrit, polyhydramnios, and serum urea level before dialysis are important predictive variables associated with fetal outcome and birth weight. Diet is another corner stone in the Pr-AKI treatment and fetal outcome gets better as a result of successful multidisciplinary management by obstetricians, nephrologists, and neonatologists, better management of anemia, and better perinatal monitoring.[11,12,51–53]

RRT on Pr-AKI has many peculiarities; being the main target avoiding excessive fluid changes and hypotension that can affect the feto-placental circulation.[11,21] There is adequate evidence that increasing the dose of dialysis/HD should be the standard of care during pregnancy because it is associated with fetal improvement, probably due to the reduction in prematurity and polyhydramnios of uremia.[12,19]

There are not enough studies to determine the optimal mode of dialysis in the pregnant patient; but intermittent HD is the most frequently chosen modality when the resource is available, although continuous hemofiltration has been used more recently since it allows volume control. On the other hand, PD placement is feasible in pregnancy and the peritoneal membrane maintains cleaning and ultrafiltration capabilities.[4]

It is important to recall that dialysis must be done early to limit/avoid the damage to the fetus, as metabolites can accumulate and cross the placenta. A successful treatment will allow to reach a higher gestational age by keeping low serum levels of urea and creatinine.[15] The threshold for the dialysis initiation in pregnancy requires considering the impact of insufficiency on fetal blood flow and uterus-placenta; early initiation of RRT may be beneficial, but there is not much evidence to guide clinical decision-making.

Enhanced HD, through longer and/or more frequent dialysis sessions, offers better maternal and neonatal outcomes. However, intrauterine growth retardation, perinatal death, polyhydramnios, premature labor, spontaneous miscarriage, as well as maternal hypertension and preeclampsia, remain common complications. This is limited to small case series and retrospective registry evaluations suggesting that only 50% of pregnancies result in a surviving baby.[30,52] In this study, the main complications were prematurity (1059), hypertension (649), and polyhydramnios (260). However, it was not possible to be more precise with the information because in several articles, the authors reported ranges of the value of a quantitative variable and not the number of subjects that met a certain classification. Another problem was that in other variables they reported the average that the newborns obtained and not the "n" on which category they belonged to.

The advantage of PD is its better tolerance during pregnancy but its collateral effects are uterine contractions, hypoglycemia, hypotension, placental abruption, postpartum hemorrhage and chorioamnionitis, risk of premature rupture of membranes, spontaneous miscarriages, vaginal bleeding, sudden fetal death, and peritonitis.[19,20] It has been reported in this context, that pregnancy in women on PD is also likely to be successful, but preterm delivery before 32 weeks of gestation and fetal distress remain the main perinatal complications of pregnant women on dialysis. Fetal distress is a consequence of acute changes in volume, electrolytes and hypotension modifying the uteroplacental circulation; therefore, it is advisable to assess vessel flow velocity with fetal Doppler.

A more frequent dialysis treatment has been recommended to increase the gestational time, the baby's birth weight, and fetal outcomes. A survey from USA dialysis centers from 1992 to 1995 reported only 40.2% of surviving babies born from women that gave birth during dialysis. From these births, 84% were premature.[52,53]

Based on the results of this review, RRT in any modality could be used as an alternative to the termination of pregnancy, with good results in pregnant women but with a reserved prognosis for the baby, which improves with the use of HD compared to use of PD. A limitation of this survey is the scarce number of publications in the last decade, a non-representative sample of five patients in one paper, the heterogeneity and missing data in some articles, and scarce results (only three articles) reporting experience with the PD modality.

Finally, the absence of specific diagnostic criteria and the overlap of clinical characteristics between various causes, with the priority of making an early diagnosis for timely treatment, justifies a multidisciplinary team of specialists in gynecology and obstetrics, nephrology, neonatology, anesthesiology, and intensive care, not forgetting specialist nurses.[11,12] The creation of protocols indicating the most appropriate therapeutic measures for a pregnant woman with Pr-AKI is mandatory.

CONCLUSION

The maternal mortality percentage among 2078 patients in HD or PD was 1.39% with 73.45% survival of the fetus in HD and 40% in PD. The three main complications are prematurity (with the consequence of low birth weight), hypertension (including preeclampsia), and polyhydramnios.

The history of use of RRT, both on HD or PD, in pregnant women with CKD, evidences their possible use as an alternative to interruption of pregnancy during AKI complication, pointing out the possibility of leading to a successful pregnancy.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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