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ORIGINAL ARTICLE

Pregnancy with Renal Disease: Present Scenario in Tertiary Care Institute in Northern India

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Abstract

Renal disease has always been a challenge for the treating obstetrician. With new advances in the management of renal disease, an increasing number of patients can continue the pregnancy and with individualization have a better outcome.

Material and Methods To analyze the pregnancy outcomes in renal disease, a retrospective cohort observational study over 5 years at a tertiary care institute in northern India was done. All the pregnant women with pre-existing renal disease of any etiology presenting at any period of gestation who consented were included and those not consenting were excluded from the study.

Results Of 62 patients enrolled, 82.26% ($n=51$) were followed,17.74%($n=11$) were lost to follow up. 58.82% ($n=30$) had to undergo termination of pregnancy and 41.18%($n=21$) had delivery after 28 weeks of gestation. The antenatal complications seen were hypertension in 15.69%, diabetes mellitus in 9.80%, anemia in 5.88%. Fetal complications included preterm delivery (42.85%) and small for gestational age babies(61.90%). Cesarean delivery was 85.71% and normal delivery in 14.29% of patients.

Conclusion Both maternal and fetal outcomes are influenced by the cause and degree of renal dysfunction. A better outcome is seen when the renal disease is under control, good antenatal follow-up, multidisciplinary approach, and timely delivery.

Keywords Pregnancy with renal diseases · Outcome of pregnancy · Creatinine levels

Introduction

Pregnancy and motherhood are now a reality for women with renal diseases with present-day medical advancements, although the fear and uncertainties about the outcome remain elusive. Difficulties increase with altered hemodynamics of pregnancy and the inability to define the renal function in pregnancy accurately with classical parameters (estimated GFR). It is estimated that almost 3% of pregnant women are affected by kidney disease globally. [1] The rising incidence of chronic kidney disease in the reproductive age group females may present a barrier to childbearing due to deteriorating renal function and decreasing fertility. This makes it necessary to understand the diseased renal physiology, various drugs used, and their effect on the mother and the fetus for better antenatal management, patient counseling, and improving outcome. [2] The outcome of pregnancy in women with renal disease depends on the following factors: the degree of prior renal impairment, the presence of chronic hypertension, proteinuria, and renal pathology. [3] We propose that individualization in management strategy is

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imperative for defining the risks and complications including worsening of renal functions, need for dialysis, transplant, pre-eclampsia, fetal growth restriction, and preterm delivery. Therefore, frequent visits for antenatal monitoring.

Methods

To evaluate the maternal and fetal outcomes in patients with a pre-existing renal disease, we conducted a retrospective observational cohort study from January 2015 to December 2019 at a tertiary care center in the department of maternal and reproductive health in northern India.

Inclusion criteria All the pregnant women with pre-existing renal disease who attended the OPD of our department from January 2015 to December 2019 and consenting were included in the study irrespective of the gestational age of presentation.

Exclusion criteria Of all the pregnant women with renal disease who attended the OPD during this study not willing to consent were excluded from the study.

The algorithm for study participants is shown in Fig. 1. Demographic factors including maternal weight and height were recorded at the first antenatal visit. The patients were classified according to the estimated glomerular filtration rate calculated at their first visit as per NKF-KDOQI guidelines calculated by the Cockcroft-Gault formula as shown in Table 1.

Management and Follow-Up

A detailed renal evaluation was done which included complete blood count, serum creatinine, uric acid, blood urea nitrogen, electrolytes, liver function tests, 24-h urine protein, and creatinine ratio (P/C ratio). Medications were reviewed and changed or stopped in consultation with the

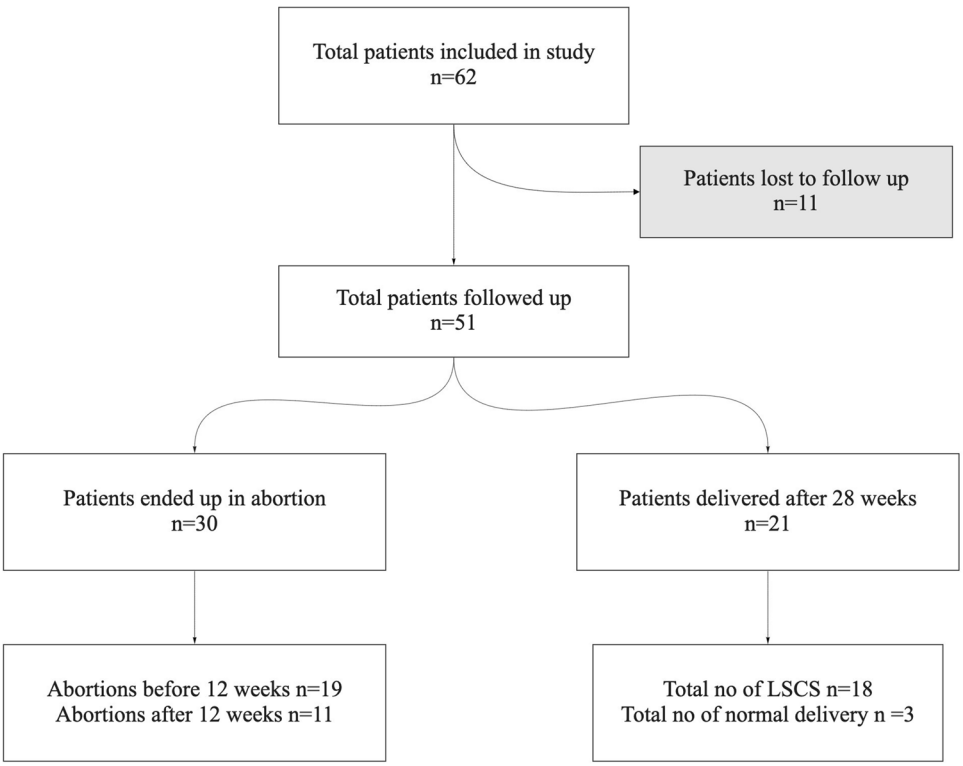


Fig. 1 Algorithm for patient recruitment

Table 1 Classification of patients according to estimated glomerular filtration rate

Stage	Description	GFR (ml/min/1.73 m^2)	MTP group ($n=30$)	Delivery group ($n=21$)
1	Kidney damage with normal or increased GFR	> 90	13.33%($n=4$)	38.01%($n=8$)
2	Kidney damage with mild decrease in GFR	60–89	6.67%($n=2$)	33.33%($n=7$)
3	Moderate decrease in GFR	30–59	20%($n=6$)	19.05%($n=4$)
4	Severe decrease in GFR	15–29	30%($n=9$)	4.76%($n=1$)
5	Kidney failure	< 15 or dialysis	30%($n=9$)	4.76%($n=1$)

nephrologist. The patient and her family were counseled about the risks to the mother, fetal outcome, need for close follow-up, and the expenditure involved in inpatient care. The decision of continuing or terminating the pregnancy was taken depending on the pre-existing renal functions, eGFR values, and couple choice. Those opting to continue the pregnancy were followed up 2 weekly till 32 weeks and weekly thereafter and more frequently if indicated. Chronic hypertension, pre-eclampsia (severe and non-severe), and superimposed pre-eclampsia were defined according to guidelines proposed by the American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy 2013.

Any change in treatment was done in coordination with nephrology advice and follow-up. Deterioration of renal function was defined by a rise in serum creatinine by 25% of the initial value. [4] Patients in stages 1 and 2 were followed up with monthly urine culture, kidney function tests including spot urine protein to creatinine ratio (P/C). 24-h urine protein to creatinine ratio was done only if the spot P/C ratio was abnormal. Patients in stages 3,4, and 5 were followed up with 2 weekly kidney function tests and spot urine P/C ratio. Dating ultrasound was done in the first trimester (irregular menstrual cycle due to dysregulation of the hypothalamic–pituitary–gonadal axis in uremic patients makes the date of last menstrual period unreliable for gestational age estimation). Targeted imaging for fetal anomalies and serum screening for aneuploidy were done between 18–20 weeks of gestation. Antenatal fetal surveillance with fetal Doppler was started at 28 weeks and a non-stress test from 32 weeks. Delivery was planned at 37-38 weeks in those with mild renal insufficiency without any signs of maternal or fetal compromise. In others, the decision to terminate the pregnancy was taken according to fetal and maternal condition.

Results

Out of 62 pregnant women with renal disease who initially enrolled, 51 followed with us, who were further classified based on estimated GFR (eGFR) as shown in Table 1. Out of these, 58.82% ($n=30$) pregnancies ended in abortion due to various indications before 20 weeks, whereas 41.18% ($n=21$) went on to continue with the pregnancy and delivered after 28 weeks as shown in Fig. 2. The demographic details of all the women including gravidity, parity, gestational age at presentation, and delivery or termination are depicted in Table 2.

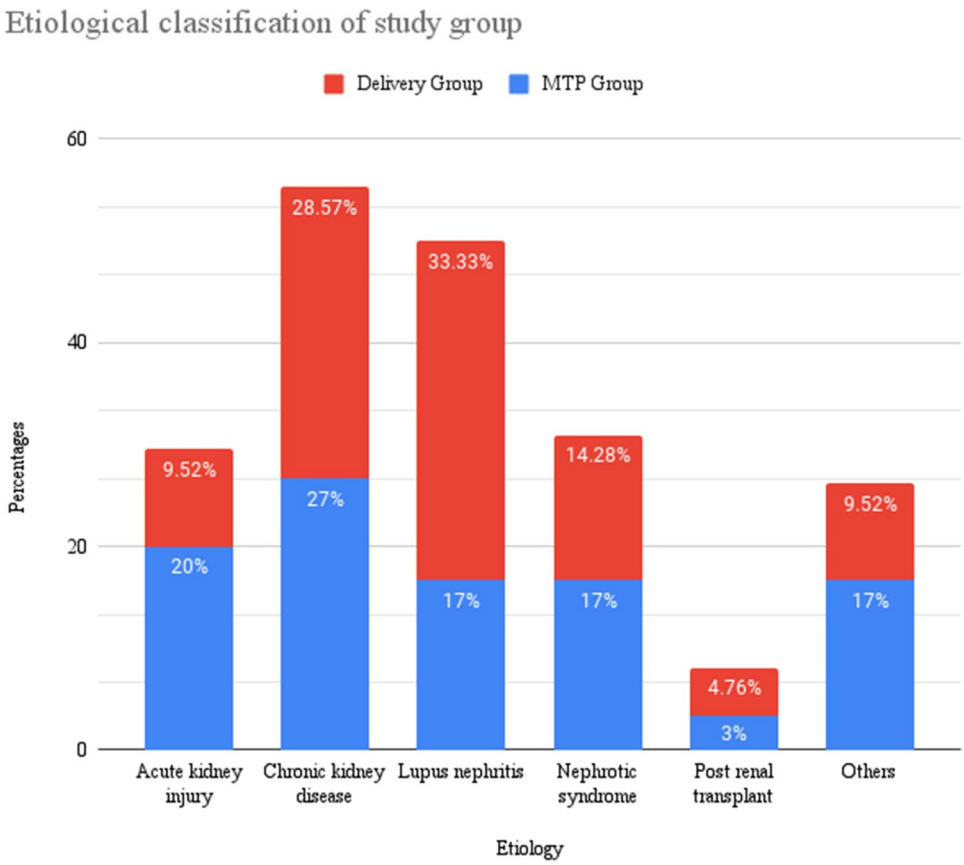


Fig. 2 Classification according to etiologies of patients in MTP and delivery group

Table 2 Features of the pregnant women with renal disease

Characteristic features	Termination of pregnancy group (mean ± SD)	Delivery group (mean + SD)	Students's t test
Age (years)	29.74 ± 5.34	30.53 ± 5.73	0.3655
Height (cms)	154.41 ± 4.36	154.81 ± 4.36	0.9050
Weight (kg)	50.12 ± 7.15	54.38 ± 10.11	0.0758
BMI (kg/m^2)	20.94 ± 2.69	22.71 ± 4.05	0.066
Gravida	2.5 ± 0	2.57 ± 1.26	0.8826
Parity	1.1 + 1.1	1.5 ± 0.75	0.4372
Gestational age at presentation (weeks)	11.26 ± 4.89		
	15.6 ± 7.27	0.016	
Gestational age at delivery /termination (weeks)	13.15 ± 5.11	36.14 ± 11.90	3.717 E-25
Creatinine (mg/dl)	2.80 ± 1.85	1.23 ± 1.02	0.000965
Hemoglobin (gms/dl)	9.05 ± 1.61	10.07 ± 2.85	0.1158
e-GFRml/min/1.73m^2)	39.03 + 36.98	86.59 + 40.26	4.1391E-05

Table 3 Fetal outcome in the delivery group

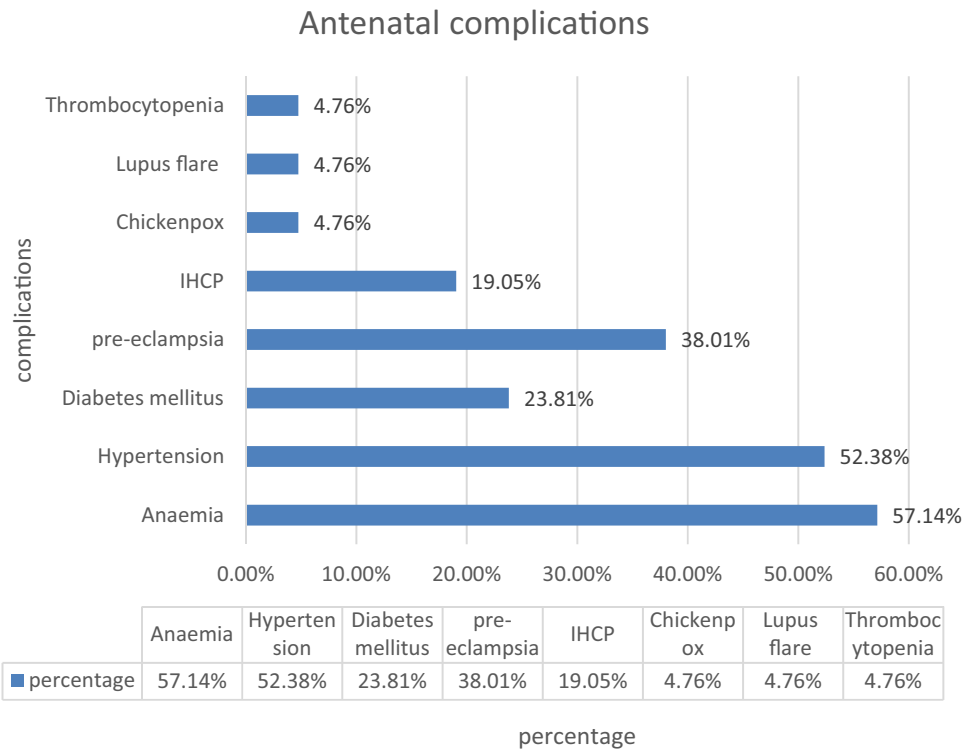
Parameters		Renal disease stage					
		Stage 1 $n=8$;	Stage2 $n=7$	Stage3 $n=4$	Stage4 $n=1$	Stage5 $n=1$	Total $n=21$
Weight (kg.)	< 1 kg:	$n=0$	$n=0$	$n=0$	$n=0$	$n=0$	$n=0$;
	1–1.5 kg	$n=0$	$n=1$;14.29%	$n=1$;25%	$n=1$;100%	$n=1$;100%	$n=4$;19.05%
	1.6–2.5 kg	$n=5$;62.5%	$n=1$; 14.29%	$n=2$; 50%	$n=0$	$n=0$	$n=8$;38.09%
	2.6–3.5 kg	$n=1$; 12.5%	$n=4$; 57.14%	$n=1$;25%	$n=0$	$n=0$	$n=6$;28.57%
	> 3.5 kg	$n=2$; 25%	$n=1$; 14.29%	$n=0$	$n=0$	$n=0$	$n=3$;14.29%
SGA (< 10th centile)		62.5% ($n=5$)	57.14% ($n=4$)	50% ($n=2$)	100% ($n=1$)	100% ($n=1$)	$n=61.90$%
Gestational age at delivery (weeks)	< 34 weeks	$n=0$	$n=1$;14.29%	$n=1$;25%	$n=1$;100%	$n=0$	$n=3$;14.29%
	34-37 weeks	$n=0$	$n=2$; 28.57%	$n=3$;75%	$n=0$	$n=1$; 100%	$n=6$;28.57%
	> 37 weeks:	$n=8$; 100%	$n=4$;57.14%	$n=0$	$n=0$	$n=0$	$n=12$;57.14%
Fetal/neonatal outcome	Neonatal morbidity	$n=1$;12.5%	$n=1$;14.28%	$n=2$;50%	$n=1$; 100%	$n=1$;100%	$n=21$;28.57%
	Neonatal mortality	-	-	-	$n=1$;100%	$n=1$;100%	$n=21$; 9.52%

In the MTP group, 60% of women had severe renal insufficiency, while 40% of women had mild to moderate disease. On the other hands, in the delivery group, 90.48% had mild to moderate disease, while 9.52% of them had severe disease (Table 3).

The women in both groups were analyzed for various etiologies (Fig. 2). The most common in the MTP group was chronic kidney injury 15.69% ($n=8$) followed by acute kidney injury 11.74% ($n=6$). Nephrotic syndrome and lupus nephritis were seen in 9.8% ($n=5$) of the women. In the delivery group, the most common etiology was lupus nephritis [$n=7$; 13.72%], the second most common being chronic kidney disease [$n=6$; 11.76%] followed by nephritic syndrome and acute kidney injury in three and two women, respectively, as shown in Fig. 2.

63.33% ($n=19$) had first trimester termination, while 36.67% (n = 11) had the termination in the second trimester. The women who delivered were 19.05% ($n=4$) before 34 weeks, 33.33% ($n=7$) between 34–37 weeks and 42.85% ($n=9$) after 37 weeks.The babies that delivered, one had extremely low birth weight (< 1000 g), 23.81%($n=5$) had very low birth weight (< 1500 g), and 33.33%($n=7$) low birth weight (< 2500 gms), while 38.09%($n=8$) were born with normal birth weight. Out of these 57.54% were small for gestational age, and 42.86% were appropriate for gestational age.

The antenatal complications seen in the women were anemia in 57.14%($n=12$), hypertension 55%($n=11$), preeclampsia in 40%($n=8$), diabetes mellitus in 9.80%($n=5$), intrahepatic cholestasis of pregnancy in 7.84%($n=4$), complications like lupus flare, chickenpox development, and thrombocytopenia were seen in one woman each as shown in Fig. 3. Indications of cesarean section were fetal distress



	Anaemia	Hypertension	Diabetes mellitus	pre-eclampsia	IHCP	Chickenpox	Lupus flare	Thrombocytopenia
percentage	57.14%	52.38%	23.81%	38.01%	19.05%	4.76%	4.76%	4.76%

Fig. 3 Antenatal complications in pregnant women with renal disease

in 23.81%, deranged dopplers and scar tenderness each in 19.04%, and other indications in 23.81%.

Women who carried on with pregnancy continued drugs to maintain disease remission like prednisolone ($n=9$) (US FDA pregnancy category C), azathioprine ($n=4$) (US FDA pregnancy category D), hydroxychloroquine ($n=6$), and erythropoietin ($n=2$) for treatment of anemia. Nine patients were on renal replacement therapy, out of which seven patients underwent termination and two of the patients of CKD underwent dialysis during pregnancy and could attain fetal viability. No maternal mortality was noted in any of the group of women. Three out of nine women on prednisolone delivered preterm (< 37 weeks of gestation). No congenital malformation was noted in any of the fetuses except a single umbilical artery in one which is not seen to be caused by any of these drugs. There were two neonates who succumbed. Neonatal mortality was seen in mothers of stage 4 and 5 kidney disease each. Both babies were very low birth weight, and the cause of death being respiratory distress in one and early-onset sepsis in another.

Discussion

The incidence of chronic kidney disease in pregnancy is increasing with recent studies reporting up to 3.3% of all pregnancies in contrast to earlier literature reporting 0.03%, due to increased survival rate with newer medications, a better understanding of the disease pathology, and successful renal transplant procedures. The parameters to assess the renal function in non-pregnant patients are not validated in pregnancy. The weight-based formula Cockroft-Gault overestimated GFR and modification of diet in renal disease formula tends to underestimate it.

A systemic review of 13 studies over four decades has shown that women with CKD appear to have at least two-fold higher risk of developing adverse maternal outcomes compared with women without CKD. A favorable outcome is seen in those with mild renal dysfunction without nephrotic proteinuria hypertension. [5] Our study also found increased adverse maternal and fetal outcomes in mothers with moderate to severe renal insufficiency and those with pre-existing hypertension.

Out of the 51 patients in our study, 58.82% ($n=30$) pregnancies ended in abortion which were because of either presentation with deranged renal function or their worsening in 70% of them; 23.33% ($n=7$) had lupus flare, and the remaining 6.67% opted for the termination because of unwanted pregnancy. The recently published PROMISSE study showed 58% adverse pregnancy outcomes and 22% miscarriage rate among this subgroup of patients with lupus nephritis, [6] which is similar to that seen in our study.

41.18% ($n=21$) went on to continue with the pregnancy and delivered after 28 weeks in all of them. Two of the

patients of CKD underwent dialysis during the course of pregnancy and could attain fetal viability. Dialysis may be initiated earlier in pregnancy depending on the glomerular filtration rate if there is an acute deterioration in renal function because of the increased risk of fetal demise. Women who initiate dialysis during pregnancy have improved outcomes compared to those who conceive on dialysis [7].

The antenatal complications seen in the patients were anemia in 57.14% ($n=12$), hypertension 15.69% ($n=8$), diabetes mellitus in 9.80%($n=5$), intrahepatic cholestasis of pregnancy in 7.84% ($n=4$). Complications like lupus flare, chickenpox development, and thrombocytopenia were seen in one patient each. Pregnancy with kidney disease is known to be associated with adverse fetomaternal outcome. On comparing the outcome in between stages 1–2 to stages 3,4, and 5, the incidence of adverse events was significantly higher in the latter group. A recent study by Piccoli et al. [1] found a higher risk of new-onset hypertension in patients with CKD when compared to controls (12% vs 5.5%). In our study, the incidence of hypertension in patients who carried on with the pregnancy was 52.38%($n=11$) and out of them, pre-eclampsia developed in 38.09%($n=8$)of them. The higher incidence of pre-eclampsia in the present study (38.09%) was consistent with that of Bramham et al. [8], where the overall incidence of pre-eclampsia was 39% (41% with mild disease and 36% in moderate to severe disease). In a study from India by Singh et al. [9], incidence of pre-eclampsia was 17.64% which was lower compared to our study. Increased incidence of pre-eclampsia in our study may be attributed to a high proportion of patients (52.38%) presenting with chronic hypertension at the onset of pregnancy. There was no case of eclampsia or abruption in our study.

The overall cesarean rate was high in our study accounting for 85.71% and normal delivery in 14.29% of patients. A study reported 33% increased odds of cesarean in kidney disease patients when compared to patients with non-kidney disease [10]. Piccoli et al. [1] also reported higher cesarean rates in patients with CKD (54.8%) compared to controls (27.2%). The high incidence of cesarean section in pregnancy with CKD in all the studies including ours may be due to the presence of severe FGR and high induction rate for maternal indications like severe pre-eclampsia or worsening renal function.

Indications of cesarean section were fetal distress in 23.81% ($n=5$) of them, deranged dopplers and scar tenderness each in 19.05%($n=4$) patients, and other indications in five of them. A high rate of preterm 42.85% was seen in our study which is similar to the study by Kendrick et al. [10], where they found 52% increased odds of preterm delivery compared to the normal population, and Pioccoli et al. who reported 37.5% of preterm births (< 37 weeks) compared to 4.9% in the control group [1].

In our study, 61.90% of newborns were small for gestational age and this was much higher than observed by Picolli et al. which was 16%. This could be attributed to the associated renal pathology and co-morbid conditions associated with the ethnic cohort.

A few of the rare cases that we saw during our study included a patient at 14 weeks with left-sided pain abdomen. On investigating it came out as renal cell carcinoma (stage II). The patient underwent a left-sided nephrectomy with adrenal gland removal at 16 weeks of gestation. Intraoperatively, this patient had an iatrogenic injury to the splenic capsule occurred which was repaired successfully. On follow-up, the patient had an uneventful pregnancy and had an elective cesarean section at 37 weeks with satisfactory fetal outcome. In patients with renal cell carcinoma (RCC), the mainstay of treatment is nephrectomy with monitoring of fetal maturity and tumor recurrence. The mode of surgery, open or laparoscopic is guided by the size, extent of the tumor, and expertise of the surgeon. Some studies have described patients being diagnosed in the second and third trimester with RCC and undergoing nephrectomy following delivery [11].

Another one was a post-renal transplant recipient 3 years back maintained on immunosuppression with cyclosporine, azathioprine, and prednisolone. The pregnancy continued well until 34 weeks when she contracted varicella infection, was treated with acyclovir, and was delivered at 36 weeks. Kidney transplantation rapidly reverses the neurohormonal abnormalities and improves libido leading to improvements in infertility [12].

Another patient was a known case of Takayasu arteritis on antihypertensives with a history of two preterm intrauterine fetal deaths. Her blood pressure was controlled on three antihypertensives. She delivered at 35 weeks because of fetal growth restriction, oligohydramnios, and increased resistance in the umbilical artery.

One patient with Sjogren's syndrome had a good maternal and fetal outcome, in contrast to studies that have demonstrated that pregnancy occurs later in life in such patients, and is usually complicated by intrauterine growth restriction and operative deliveries [13].

Conclusion

Pregnant women with kidney disease pose a significant challenge for the treating obstetrician and may result in early obstetrical intervention in form of termination and a higher incidence of abortions as highlighted in the present study. A high proportion of fetal wastage and maternal morbidity is generally seen in such cases. Hence, in all patients with kidney disease, planning for pregnancy, the pre-existing disease

should be optimized before conception, and the extent of renal pathology determined. These women should be cared for by a multidisciplinary team that includes midwives, specialists in maternal medicine, nephrologists, neonatologists, anesthesiologists with delivery planned ideally in a tertiary care center all facilities of ICU, dialysis, and NICU are present and may result in better pregnancy outcomes.

Author contributions: AG conceptualized the idea, managed the pregnant women, revised the manuscript for intellectual content, statistical analysis. KD managed the pregnant women, drafted the manuscript, statistical analysis. GS managed the pregnant women, initial drafting, data collection. RG managed pregnant women, data collection.

Financial disclosures None.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical statements All procedures followed were in accordance with the ethical standards of responsible committee on human research (institutional and national) and with the Helsinki declaration of 1975, as revised in 2008.

Informed Consent Verbal consent was obtained from all respondents to be included in study

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