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Original Research Article

Chronic kidney disease in pregnancy and fetomaternal outcome

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ABSTRACT

Background: Chronic kidney disease is a heterogeneous group of renal dysfunctions with complex and varied presentations in pregnancy. With a long asymptomatic course, timely diagnosis and management is crucial for fetomaternal wellbeing.

Methods: A retrospective cohort study over a period of 3 years and 4 months included all obstetric in patients with known or newly diagnosed renal disorders. Maternal outcome was measured with regard to biochemical parameters presence /absence of proteinuria, hypertension, mode of pregnancy termination and complications. Fetal outcome was noted with respect to antenatal complications, weight, Apgar, NICU stay. Computation of results was done using percentages, mean and proportions.

Results: Out of 13 women studied, 53.8% were pre-diagnosed cases of renal dysfunction and 46.2% were diagnosed during pregnancy. 38% had proteinuria at first visit and 50% remained so even after delivery. 60% had history of pregnancy induced hypertension in their previous pregnancies. Secondary hypertension and superimposed preeclampsia were seen in 30% and 38% cases respectively, with only one patient requiring magnesium sulphate prophylaxis in post-partum. Cardiac dysfunction was found to be coexisting in 15.3% cases with pre-existing renal lesion. Intrauterine growth restriction was seen in 61.5% cases Average fetal weight was 2.26kg with 30% having NICU stay. 30.6% had preterm delivery. Mode of delivery was caesarean section in 46% cases.

Conclusions: Pregnancy with CKD is a high-risk pregnancy with adverse fetomaternal outcomes. For optimal pregnancy outcomes, an expert multidisciplinary team is required. With limited studies in south Asian population, there needs to be an upgradation in registry system.

Keywords: Acute kidney failure, Cardiac failure, Obstetric nephrology, Pregnancy, Premature, Stillbirth

INTRODUCTION

The urinary system undergoes significant structural and functional changes during normal pregnancy. Pregnancy has been regarded as a high-risk phase to women with underlying renal disease.^{1,2} In normal pregnancy as the cardiac output increases, there occurs an increase in the renal plasma flow and glomerular filtration rate, leading to hyperfiltration. Those with underlying renal disorders are unable to adapt to these physiological changes. Hence leading to unfavourable fetomaternal outcomes.³

CKD is a heterogeneous group of renal dysfunctions with a GFR below 60 ml/min, lasting for at least 3 months".^{4,5} Due to its complex presentations, recently the term "obstetric nephrology" has been proposed to represent CKD in pregnancy.⁶ Globally its prevalence among women is estimated to be 11%-13%.⁷⁻⁹ In India, prevalence of CKD is found to be higher than their male counterparts i.e. between 16.3% and 19.1%.¹⁰⁻¹³ Specifically, prevalence among women of reproductive age worldwide is 0.1% to 3%.¹⁴ It carries a long asymptomatic period till significant renal damage occurs

and symptoms appear. Hence there is a need to keep a high level of suspicion to make an early diagnosis since at all stages of CKD are associated with increased morbidity and mortality.

Conventionally, CKD is staged according to the worsening of glomerular filtration rate.¹⁵ Recent, guidelines stage chronic kidney disease (CKD) according to levels serum creatinine. Mild, moderate, severe as creatinine levels <1.5mg/dl, 1.5-3.5mg/dl, >3.5mg/dl respectively.^{16,17} In normal pregnancy, due to hyperfiltration and increased creatinine clearance, the normal values is up to 0.5mg/dl. Any values greater than 0.9mg/dl corresponds to underlying renal pathology and warrants detailed evaluation. Patients with an estimated GFR \geq 1.4mg/dl are at increased risk of progressive worsening of renal function.¹⁸ Certain pregnancy specific renal insult can complicate the already diseased kidneys of CKD patients.^{19,20} They may present with acute kidney injury (AKI) in post-partum and their progression depends upon the severity of underlying renal dysfunction irrespective of aetiology.^{21,22} With limited studies in Indian Subcontinent, there needs to be further studies to demonstrate the fetomaternal effects with the individual etiological subtypes.

METHODS

A retrospective cohort study was conducted among inpatient obstetric population of PGIMER and Dr. RML Hospital over a period of 3 years and 4 months (January 2016-May 2019). Data was retrieved from case files taken from hospital medical record department. Cases included under study comprised of all inpatient obstetric population with known or recently diagnosed renal disorders irrespective of underlying etiology. Renal dysfunction was defined by deranged biochemical parameters (blood urea in mg/dl, serum creatinine in

mg/dl and serum uric acid in mg/dl) for at least 3 months, existence of proteinuria and presence /absence of complications like hypertension, cardiac failure, confirmation by presence of renal biopsy in prediagnosed cases. Observations with regard to all findings were done at time of first visit, during admission to hospital and during discharge. Among it, proteinuria was assessed subjectively using conventional dipsticks using PTBP (polytetraabromophenyl) as indicator. Those with proteinuria were subjected to confirmatory tests in form of 24 hour urinary protein (mg/day). Urine routine microscopy and urine culture sensitivity were noted. Haemoglobin levels were noted for grading of anaemia (mild 10-11gm/dl, moderate 7-9gm/dl, severe <7gm/dl). Blood pressure was noted as per records. As per hospital protocols, method followed included measurement in sitting position in left arm using mercury sphygmomanometer after 5 minutes of rest, using 140/90mmHg as cut off for defining hypertension, cardiac dysfunction confirmed after echocardiography. Note was made of obstetric history, medical/surgical history and family history. Intrapartum or postpartum complications. Obstetric history included time to first conception, gravida, parity, abortions, live births, still birth, ectopic, gestation age at termination and its mode, complications if any. Foetal outcome was defined by fetal weight measured in nearest kilograms on spring type weighing machine, Apgar score recorded by attending paediatrician, NICU stay if any and its duration. Computation and analysis of results was done using percentages, mean and proportions in tabular forms..

RESULTS

Out of 13 women studied, mean age was observed to be 25.69 years, whereas mean weight was 57.53kg. All patients had non consanguineous marriages and conceived spontaneously within 1 year of married life.

Table 1: Distribution of pregnancy outcome as per serum creatinine levels at first visit.

Serum creatinine levels (at first visit) mg/dl	Number of patients at first visit	Spontaneous abortion	IUGR	Preterm delivery	NICU stay	Perinatal death
<0.5	4	1	1	1	1	0
0.5-0.9	6	2	5	1	2	0
>0.9	2	2	2	0	1	0

All, except one, pregnancies were booked and under regular follow up in antenatal clinics. Women were found to have their first visit to hospital in first, second and third trimester as 33.3%, 58.3% and 8.3% respectively. Among women booked at antenatal clinic, 7 out of 13 (53.8%) were already diagnosed cases of renal dysfunction whereas rest (46.2%) were diagnosed during antenatal visits. Out of multiparas, 60% had history of

pregnancy induced hypertension in their previous pregnancies.

To begin with 38% of the patients had proteinuria at their first visits. Whereas, 14% developed during pregnancy and 50% of women studied remained hypertensive in the post-partum phase irrespective of aetiology. Associated co-morbidities were observed in the form of secondary/renal hypertension and superimposed

preeclampsia syndrome seen in 30% and 38% cases respectively. In postpartum phase, only one patient received magnesium sulphate prophylaxis for 24 hours. Among patients, only one presented with severe complications in form of cerebrovascular accident. Proteinuria as an indicator of renal function was found to be present in varying amounts in 38% patients at the first visit. This persisted till delivery and worsened in 46% cases. Among patients with pre-existing renal disease, cardiac dysfunction was diagnosed to be coexisting in 15.3% cases. On basis of obstetric history, 80% cases of spontaneous abortions were found to be present in those with high serum creatinine levels at the first visit. Of these, only 1 (7.6%) had associated Mullerian anomaly in form of unicorn ate uterus with normal renal anatomy. With regard to fetal wellbeing, intrauterine growth restriction (as confirmed by ultrasound) was seen in 61.5% cases. Among term pregnancies, 1 out of 9 (11.1%) landed up with poor biophysical profile, for which induction of labour was done. Average fetal weight was observed to be 2.26kg. Of them, 4 out of 13 (30%) had NICU stay due to low birth weight and TTN (transient tachypnoea of new born) (Table 1).

Table 2: Distribution of number of deliveries with gestational age at termination.

Gestational age (in weeks)	Gestational age	Number of deliveries
<33+6	Early preterm	2
34-36+6	Late preterm	2
37-38+6	Early term	9
39-40+6	Full term	0
>41	Post dated	0

Table 3: Percentage distribution of severity of anaemia during course of pregnancy with CKD.

Severity of anaemia	At first visit	At admission	Postpartum
Severe <7gm/dl	7%	7%	0
Moderate 7-9gm/dl	46%	38%	46%
Mild 10-11gm/dl	38%	30%	38%

Majority of patients delivered at early term (61.5%), whereas remaining (30.6%) had preterm delivery-15.3% as early preterm, another 15.3% as late preterm. Also, 1 out of 13 (7.6%) had preterm intrauterine demise. Among patients, spontaneous onset of labour was observed in 10 out of 13 (30%) cases, whereas 3 of 13 (23%) were induced by PGE2 gel due to obstetric indications. Of the induced labours, only one had emergency caesarean due to non-progress of labour. Elective caesarean was carried out in 38% cases, including the one which was done on request. Another 8% included preterm emergency caesareans that led to iatrogenic prematurity (Table 2).

Among those operated, 16% had SSI (surgical site infection).

At first antenatal visit, anaemia was observed to be mild, moderate, severe in 46%, 38%, 7% cases respectively. Percentage of cases found to be anaemic at first visit showed improvement further at their admission and discharge (Table 3).

Average duration of stay was observed to be 17.9 days.

DISCUSSION

In today's world, with demographic expansion and increased high risk behavior, probability of death from CKD among young adults is increasing.²³ Supporting the evidence, we observed the average of CKD cases studied was 25.6 years at presentation. With the lack of an updated registry system, the rising prevalence of CKD in young productive population gives a socioeconomic impact in developing countries like India. In this signifies a need for early and accurate diagnostic and treatment modalities to especially those at risk. But irrespective of ante-natal events, post-partum decline in kidney function has been observed.²⁴

Previously, it was considered for the women with CKD to avoid pregnancy and allow termination in fear of getting the disease worsened.¹⁴ But with advances in obstetric care, pregnancy can be continued under supervision of a nephrologist and mode of termination can be decided as per obstetric point of view.

CKD is known to be associated with decreased fertility and poor reproductive outcomes, mostly attributed to the hypothalamic pituitary axis dysregulation.²⁵ Whereas we observed 100% spontaneous conception rate in our study population, with all of them conceiving within the first year of marriage.

Preterm births refer to those before 37 weeks, whereas prematurity refers to immaturity to attain an organ functioning. Embryologically, 60% of nephrons differentiate in third trimester and delivery before term impairs this development process.²⁶⁻²⁸ Casey C et al, observed that preterm and early term birth had nearly twofold and 1.3-fold higher risks of developing CKD in adult life, respectively, compared with full term birth.²⁶ We also observed all deliveries in these two categories only i.e. 61% early term and 30% preterm deliveries, none falling in full term or postdated category.

Seema C et al, conducted a retrospective analysis and identified 85% cases to be preterm deliveries with fetal survival rates 77%.²⁹ In this regard, our study group had fewer i.e. 38% of preterm deliveries (including a preterm intrauterine device. With only one perinatal mortality noted, the fetal survival rate was significantly higher making up to 93%. This can be attributed to better healthcare facilities and nursery care.

In same study, it was observed that anemia was diagnosed in 46.1% cases and 7.7% of them required multiple blood transfusions. However, we observed anemia to be present among 76% cases at admission, out of which 7% required blood transfusion.

Mode of termination in our patients was individualized. Among cases, 30% went into term spontaneous onset of labor and had normal obstetric outcome. Whereas our cesarean rate was 46%, which was slightly higher than seen in above study, with 30% incidence.

Anemia is highly prevalent in patients with CKD, reported in up to 50% of patients and severity depends upon the degree of renal dysfunction.³⁰ In combination with dietary iron malabsorption and losses, erythropoietin deficiency is the main factor.³¹ Another reason cited is reduced availability for hematopoiesis due to reticuloendothelial blockade. In CKD patients, anemia is associated with adverse events (cardiovascular disease, infection, hospitalization, and mortality).³²

Kidney disease improving global outcomes (KDIGO) defines severe anemia as hemoglobin ≤ 9 g/dl because it is the level at which symptoms onset occurs.^{33,16} Accordingly, Katherine G et al, observed 13.7% cases of severe anemia, with mean length of stay being 6.4days. In contrast we found a greater incidence of anemia i.e. 46% of patients at admission (mean hemoglobin of 8.3gm%). Mean length of stay hence was observed in our case to be 17.9days. Apart from duration of neonate nursery stay, this was mainly due to maternal surgical site infection.³⁴

Chronic kidney disease (CKD) is a major contributor to cardiovascular (CV) mortality.³⁵ As the renal disease worsens, there is element of cardiac hypertrophy and fibrosis. This has been attributed to oxidative stress and reduced nitric oxide availability in cardiac myocytes.³⁶ Izumaru K et al, observed cardiac remodeling in form of left ventricular hypertrophy (LVH) and fibrosis, a feature common in CKD.³⁷ This impedes the diffusion of oxygen and leads to apoptosis of cardiomyocytes and displacement of collagen fibers. Cardiac failure is becoming a leading cause of death in patients with CKD. We also observed 15% cases to be associated with preexisting cardiac lesions in form of rheumatic heart disease (mitral stenotic component) and dilated cardiomyopathy. However, their course was stable during pregnancy and postpartum. This concept highlights the need for routine screening of CKD patients for cardiac wellbeing.

Misra et al, observed 100% rate of preterm delivery in all patients with a diastolic blood pressure >100 mmHg. They observed that of these, 35.5% cases of uncontrolled hypertension had iatrogenic preterm deliveries.³⁸ Serum creatinine worsened in 32.5%, more in those with high pre pregnancy values. Similarly, Seema C et al observed that 90% women developed hypertension during pregnancy in which 40% had mild hypertension and

43.3% had severe hypertension requiring drug therapy.²⁹ In meta-analysis conducted by Zhang JJ et al, greater odds of preeclampsia, premature delivery, small for gestational age/low birth weight were obtained in the patients with CKD.¹⁴ O'Shaughnessy MM et al made an observation of 33% of pregnancies complicated by preeclampsia and 27% by persistent increase in serum creatinine. Our findings were similar to the above studies as we found 38% of cases developed preeclampsia requiring medical therapy. Out of these, 40% had term deliveries, 40% had iatrogenic prematurity due to uncontrolled blood pressures and IUGR and 20% had spontaneous preterm premature rupture of membranes. But in contrast with above study, we observed 61.5% had worsening of serum creatinine levels during pregnancy. Although none required dialysis, there arises a need that these patients should be meticulously followed post-delivery to timely manage and prevent progress to (End stage renal disease) ESRD.

O'Shaughnessy MM et al, studied on a obstetric population comprising 13.3% cases of membranous nephropathy, 9.3% of minimal change disease and 3.7% cases of focal segmental glomerulosclerosis.³⁹ Among them, 13% of pregnancies resulted in perinatal death and 48% preterm deliveries. Whereas we observed a greater incidence of FSGS, minimal change disease and membranous nephropathy in 7.6% and 15.3% cases respectively.

Presence of a solitary kidney can be due to congenital agenesis, contralateral nonfunctioning kidney or spontaneous involution of a congenital dysplastic kidney. Renal agenesis refers to failure of embryonic renal bud differentiation. Steele SE et al, observed an incidence of 57.6% pregnant women with congenital single kidney. None had hypertension or proteinuria in first visit. Among them, urinary tract infection complicated 50% of pregnancies and 35% developed pre-eclampsia during course of their pregnancy.⁴⁰ We studied 5 out of 13 (38%) cases having pre-diagnosed solitary kidney. Of these 20% were known renal hypertensive and consequently developed superimposed preeclampsia and 20% suffered from symptomatic UTI (E. coli >105 CFU).

CONCLUSION

Pregnancy with CKD is considered as a high-risk pregnancy. Despite recent advances in obstetric care, incidence of adverse fetomaternal outcome continues to be high in these women. For optimal pregnancy outcomes, an expert multidisciplinary team is required for their periconceptional disease optimization and follow up. Adverse effect of individual subtype of renal diseases in pregnancy requires further large studies. With hardly any studies on chronic kidney diseases in south Asian population specifically, there needs to be an updated registry system among the health care providers for a broader view of this health problem.

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