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ORIGINAL ARTICLE

Pregnancy Check Point for Diagnosis of CKD in Developing Countries

A. Kaul[1] · D. Bhaduaria[1] · M. Pradhan[2] · R. K. Sharma[1] · N. Prasad[1] · A. Gupta[1]

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About the Author

Dr Anupma Kaul is a Additional Professor in Department of Nephrology at Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow. She has wide experience in field of nephrology for last 18 years. Her area of interest has been obstetric nephrology focussing on preventive aspect, clinical nephrology, especially diabetic kidney disease and acute kidney injury. She has over 60 papers on her name in various index journals.

Dr Anupma Kaul, Additional Professor, Department of Nephrology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India; Dharmendra Bhaduaria, Associate Professor, Department of Nephrology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow; Mandakini Pradhan, Professor, Department of Maternal and Reproductive Health; R. K. Sharma, Professor, Department of Nephrology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow; Narayan Prasad, Professor, Department of Nephrology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow; Amit Gupta, Professor, Department of Nephrology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow.

✉ A. Kaul
essbhat@yahoo.co.in

[1] Department of Nephrology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India

[2] Department of Maternal and Foetal Medicine, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India

Abstract

Objective Evidences suggest that females with CKD are associated with high risk of maternal and fetal complications. Early referral in CKD with pregnancy for specialist care may prove useful for maternal and fetal outcome.

Methods Study looked for assessment of impact of CKD detection at the time of pregnancy and its impact on fetal and maternal outcome.

Results A total of 465 females were retrospectively evaluated for renal status during their pregnancies, 172 females were unaware about their renal illness at the time of pregnancy, while 208 females were under regular obstetrical and nephrological follow-up during their pregnancy. 44.1% of these females in both groups had GFR < 60 ml/min. Preeclampsia was observed in 17.6% of planned pregnancies, while it was observed in 47.5% of unplanned pregnancies. Worsening of renal failure during and following pregnancy was observed among all stages of CKD,

and there was greater decline in GRF with progression to ESRD earlier during or after pregnancy among unplanned pregnancies. Planned pregnancy group had better fetal outcome. Low birth babies weighing < 2500 g in unplanned group were much higher than in planned pregnancies. *Conclusions* Chronic kidney disease is often clinically silent until renal impairment is advanced. Pregnancy can be a check point for detection of renal disease and managed appropriately for better maternal and fetal outcome.

Keywords Pregnancy · Chronic kidney disease · Maternal outcome · Foetal outcome · Dialysis dependancy

Introduction

Pregnancy is challenging among females with chronic kidney disease (CKD) and requires multidisciplinary approach comprising of obstetrician, nephrologists and neonatologist. Chronic kidney disease is often clinically and biochemically silent until renal impairment is advanced. Symptoms are unusual until the glomerular filtration rate declines to < 25% of normal. Some women are found to have chronic kidney disease for the first time during pregnancy. Around 20% of women who develop early preeclampsia (≤ 30-week gestation), especially those with heavy proteinuria, have previously unrecognized chronic kidney disease [1]. These diseased kidneys may be unable to adapt to the normal physiological changes of pregnancy leading to poor maternal and fetal outcome [2]. Evidences suggest that females with mild renal impairment with normal BP and little or no proteinuria have good maternal and fetal outcomes, with little risk of accelerated progression toward ESRD or preterm delivery. However, those pregnancies among CKD population have shown poor maternal and fetal outcomes [3, 4]. Jones and Hayslett [2] observed that CKD was associated with increased risk of adverse pregnancy outcomes, especially among pregnancies with moderate or severe renal function impairment. More than one-third experience an irreversible decline in GFR and 10% progress to end-stage renal disease (ESRD) by 12 months postpartum [5]. These findings highlight the important need for early identification of CKD, preconception counseling, preconception review of medications and early referral of pregnant patients with CKD for specialist care.

Studies have suggested that the risk of deterioration in maternal renal function is increased mainly when conception has occurred at a plasma creatinine concentration in excess of 200 mol/L (equivalent to eGFR < 25–30 mL/min/1.75 m^2) or in the setting of poorly controlled hypertension [6]. Whether such deterioration represents an acceleration of renal failure progression or merely the natural history of the underlying chronic kidney disease which has not been conclusively established needs to be evaluated. Women, especially in developing countries like India, conceive without preconception evaluation and have no regular follow-up under an obstetrician; therefore, CKD females with pregnancy become subjected to risk of accelerated decline in renal function and poor pregnancy outcomes.

Aims and objective—The present study looked into those females presenting with chronic kidney disease (various stages) and assessing the impact of CKD detection at the time of pregnancy and its impact on fetal and maternal outcome, highlighting the need to address the influence of pregnancy on the underlying kidney disease and the kidney disease affecting the outcome of pregnancy.

Materials and Methods

This retrospective observational study of female patients with CKD who were assessed about their pregnancy outcomes, their awareness of illness at the time of pregnancy and its outcome on renal as well as pregnancy outcomes conducted at tertiary care health-care center from northern part of India from January 2011 to January 2016.

CKD was defined as per standard definition of CKD by kidney disease outcomes quality initiative guideline [7].

Hypertension

It was defined if there were two blood pressure measurements > 140/90 mm Hg or there was history of antihypertensive drug use. If the hypertension was observed before 20 weeks of gestation with proteinuria or renal failure, hypertension was considered to be renal in origin.

Preeclampsia

It was defined as abrupt onset of hypertension after 20 weeks of gestation associated with the appearance of proteinuria with protein excretion > 300 mg/day. All females with history of hypertension or proteinuria at start of pregnancy and had doubling of proteinuria associated with worsening of hypertension after 20 weeks [8, 9].

All female patients in child-bearing age group (18–45 years) with the first time diagnosis of "chronic renal failure" or "chronic kidney injury" either before or during pregnancy were identified, and degree of awareness about the disease and its implication on maternal and fetal outcomes and management of pregnancy and future outcome were looked for.

Cases

Those pregnancies where the patient was not aware about the renal disease at the time of pregnancy with no meticulous follow-up during pregnancy by the obstetrician or nephrologists were considered cases.

Control

Those pregnancies where the obstetrician had explained about the illness and precautions and meticulous measures taken for successful pregnancy outcomes were identified as control.

Among females who were diagnosed with CKD at the time of conception and under regular follow-up were assessed about progression of CKD using GFR assessment. Glomerular filtration rate (GFR) was estimated using the CKD epidemiology collaboration equation and expressed in ml/min/1.73 m^2 of body surface area [10]. Rate of progression was assessed from the first clinical or laboratory evidence of renal dysfunction assessed by GFR and a decline during and or after pregnancy in ml/min.

Patient data were retrieved from the computerized hospital-based electronic information system and patient record files. All records of the patient's history, physical examination, laboratory investigations and discharge reports, their clinical presentation, etiological diagnosis and outcomes were evaluated and examined by two nephrologists. A clinical and histopathological diagnosis was made after scrutinizing all the details.

Their detailed history regarding symptomatology related to renal disease, pregnancy evaluation regarding renal disease and detection of renal disease from time from pregnancy was assessed, and any association with worsening of progression was assessed following pregnancy.

Outcome Criteria

The primary maternal outcome was decline in renal function after pregnancy at 6 weeks after delivery at completion of puerperium when the physiological changes related to pregnancy are settled. The other outcome criteria were doubling of the serum creatinine and 50% decline in GFR or ESRD at 1 year of follow-up. The fetal outcome was analyzed in terms of full-term and preterm delivery, stillbirth and low birth weight. Among females who were unaware of their illness at time of pregnancy were assessed for any decline in renal function in terms of doubling of serum creatinine and or 50% decline in GFR or ESRD.

The primary maternal outcome was assessed in terms of decline in renal function from the time of detection, i.e., before or during pregnancy, and the clinicians and females awareness of the illness and its implication on maternal management with its association with maternal outcome, i.e., renal as well as overall outcome.

Fetal outcome was analyzed in terms of preterm and full-term delivery, stillbirth and low birth weight. Stillbirth was defined as the occurrence of intrauterine fetal death after 24 weeks of gestation. Preterm delivery was defined as a live birth before the 37th week of gestation. Pregnancy was considered successful if it resulted in a live infant who was discharged from the hospital. Low birth weight is defined as a live-born infant weighing < 2500 g.

Statistical Analysis

All the data were analyzed using statistical package for the social sciences (SPSS) 16 statistical software (SPSS Inc., Chicago, Illinois, USA). All data are expressed as mean $\pm$ standard deviation. Student's t test was used to compare the mean values between two groups. One-way analysis of variance and Bonferroni test were used to compare the differences in mean values of > 3 variables. The Chi-square test was used to compare the categorical variables between the groups. $P < 0.05$ was considered significant.

Results

A total of 465 female's patients presented in nephrology OPD from January 2014–January 2016 with chronic renal failure (CKD) and were retrospectively looked into their pregnancy outcomes and renal disease.

Demographic Profile (Table 1)

Among 465 females, 85 pregnant ladies were not in follow-up of any obstetrician and had home delivery, while among the remaining 380 females, 172 of them despite being under obstetrician follow-up had no ante-natal or postnatal evaluation about their renal illness, i.e., serum creatinine, urine examination or ultrasound KUB region available. A total of 208 females who were aware about their renal disease during pregnancy were under regular obstetrical and nephrological follow-up.

Detailed evaluation retrospectively identified 382 females giving history of edema, headache, recurrent urinary tract infections and nocturia in them.

Pregnancy Outcomes (Table 1)

Among 380 patients, 172 females during pregnancy had awareness about their renal illness and were in regular follow-up with the nephrologists/obstetrician during pregnancy. All patients had in-hospital delivery. According to

Table 1 Clinical and demographic profile of CKD patients during pregnancy

Parameters	Awareness at the time of pregnancy ($n = 172$)	Unaware about CKD at time of pregnancy ($n = 208$)
Average age at time of pregnancy	26.7 ± 5 years	27.4 ± 4.7 years
Average number of pregnancy	3 ± 1	4/± 1
GRF at presentation		
Stages 1–2 (> 60 ml/min)	96	117
Stage 3 (30–60/min)	47	57
Stage 4 (15–30 ml/min)	29	34
Stages 3 + 4 (< 60 ml/min)	76	91
Proteinuria		
Subnephrotic	114	138
Nephrotic	58	70
Urinary tract infection	64	68
Hypertension	125	146
Preeclampsia	30	78
Basic disease		
Chronic glomerulonephritis	58	72
Chronic interstitial nephritis	72	79
ADPKD	7	5
Stone disease	5	8
Others	30	44

GFR stages 1 and 2, CKD was observed among 86 pregnancies, while 48 were in stage 3 and 26 were in stage 4. GFR < 60 ml/min was 76 in the aware group, while it was 91 in the unaware group. 33.7% had presented with nephrotic range proteinuria similar in both the groups, while 125 females had hypertension during the first or second trimester of pregnancy. Despite regular and optimized follow-up, worsening edema was observed in 37% and urinary tract infections requiring admission were observed in 6% pregnancies. 34% of these ladies required admission during pregnancy for various reasons.

Among the 208 females who belong to the unaware group, were not in regular follow-up under a proper obstetrician and or nephrologists as they were unaware about their renal illness. This population was not judiciously managed during pregnancy due to lack of awareness by the patient and or the obstetrician about the underlying renal disease.

On retrospectively observing their baseline values, 37.5% had presented with preeclampsia and two patients had eclampsia at 32 weeks of gestation. Totally, 46 patients required early admission before termination of pregnancy for worsening hypertension, worsening edema, recurrent infections. That is, 12% had recurrent urinary tract infection with early fetal loss in four of them. In the unaware group, 142 underwent normal delivery, while early termination was required in 46.7% of them. Antepartum/postpartum bleeding was observed in 12.6%, while infection was encountered in 15.2%.

In the planned pregnancy group, preeclampsia was observed in 17.6% of planned pregnancies, more evident among females with GRF < 60 ml/min, i.e., 12.6% as compared to 29.5% between the aware and unaware groups, respectively. A total of 78 females underwent caesarian section, while 132 had normal delivery. Those pregnancies which were in regular follow-up of the obstetrician underwent caesarian section, while the rest had presented with worsening hypertension, breathlessness and worsening edema requiring early termination in about 24% of them. Ante-partum/postpartum bleeding was observed in about 4.5% of pregnancy.

Renal Outcomes (Table 2)

Decline in GFR was assessed from time of the first detection of renal failure to time after or any time when patient became aware about her renal illness.

Those pregnancies which were planned and monitored judiciously had better outcome. Worsening of renal failure during and following pregnancy was observed among all stages of CKD, but was more evident when GFR < 60 ml/min. This decline in GFR was much less as compared to those pregnancies in unaware group where meticulous follow-up was not done. There was greater decline in GRF among all stages with progression to ESRD earlier as compared to aware group. Those females who were having presumably glomerular illness faired poorly than ones with interstitial illness among both the groups.

Table 2 Renal outcomes during or and following delivery or at time patient becomes aware of renal disease

Parameters	Awareness at the time of pregnancy ($n = 172$)	Unaware about CKD at time of pregnancy ($n = 208$)
Average fall in GFR at follow-up after delivery or at the time the patient is aware		
Stages 1–2	86	71
Stage 3	48	63
Stage 4	26	41
Stages 3 + 4	84	101
Nephrotic range proteinuria at follow-up	69	96
ESRD	12	31
Worsening of GFR	51	87
Average time to dialysis from pregnancy	5.1 ± 2.5 years	2.3 +/1.2 years
Worsening of hypertension	29	65
Delivery	131	111
Full term	41	97
Preterm		
Fetal outcome		
Alive	147	90
Still birth	74	118
Low birth	45	98

Fetal outcome (Table 1)

In the planned pregnancy group, foetal outcomes were better with 147 had 147 live births as compared to 74 among unmonitered group. 24% had preterm delivery among planned pregnancy group, while 26% had babies < 2500 g. However, in the unaware group, 56.7% had still births, while preterm delivery was observed in 46.7% pregnancies. A total of 96 pregnancies had low birth babies weighing < 2500 g.

Full-term pregnancy was higher among ladies with > 60 ml/min GFR in both the groups.

Discussion

The prevalence of CKD in pregnancy is reported rarely, especially in developing countries. This discrepancy may be due to several reasons besides underreporting. The prominent ones could be: (1) Pregnancy happens in young population and is expected to be healthy. (2) Pregnant females are not routinely screened for renal dysfunction. (3) Females with substantial renal insufficiency or renal failure are either beyond child-bearing age or infertile. Hence, it is essential to screen all females during pregnancy for CKD to prevent progression of renal disease besides poor maternal and fetal outcome.

A multidisciplinary approach is required to manage such pregnancy for better foetal and maternal outcomes. In such circumstances, multidisciplinary process is intimidated which can help in careful management of maternal and fetal outcome.

Every pregnancy should be thoroughly investigated and evaluated, and in those females with CKD, prepregnancy counseling is recommended. Hypertension, proteinuria and teratogenic medications, e.g., ACE inhibitor usage, are prevalent among these females and need to be optimized before conception. There is increase risk of maternal and fetal outcomes among pregnant CKD patients and needs to be communicated and understood well by them before conception [10]. In our study population, 18.2% had home delivery with no ante-natal checks even. Despite being under obstetrician follow-up, 44.7% were not aware of the renal disease at the time of pregnancy, suggesting that prepregnancy evaluation as well as counseling is indeed essential for better fetal and maternal outcome. Pregnancies which were planned had better outcome in terms of fetal and maternal outcomes. Worsening of GFR was observed in 29.6% of pregnant females, while it was 41.85% among females who were unaware. Preeclampsia was observed in 17.2% among females who were aware as compared to unaware females which was 37.5%. Higher preterm and low birth babies were born to females unaware about their renal illness. Time to ESRD was faster among unaware females as compared to those ladies who were aware about their illness.

Clinical Marker of Renal Disease During Pregnancy

Hypertension during pregnancy is associated with decline in GFR which is more profound among females with already impaired renal functions [11]. This observation was evident in our study where females unaware about their renal disease had worsening of hypertension in 31.8% as compared to aware females, i.e., 17.05% with worsening of GFR following delivery.

34.1% had nephritic range proteinuria at the baseline among the aware group, while it was 34.3% among the unaware group; however, there was worsening of proteinuria during and following pregnancy in both groups, but more marked in unaware group to 47.15% with higher number developing preeclampsia and worsening renal function. The literature suggests asymptomatic pregnant women with proteinuria > 500 mg/day, not previously known renal disease and no evidence of preeclampsia, 20% of them progressed to ESRD at a median time of 5 years. (22). When proteinuria exceeds 1 g/day, there is a greater tendency for accelerated GFR decline and nearly a twofold higher incidence of ESRD [7].

Renal failure at the time of presentation has great impact on future maternal and fetal outcome as observed in our study females with advanced renal disease fairing poorly in terms of fetal and maternal outcome. Our study observed that among planned pregnancy group, 24% had preterm delivery, while 26% babies born were weighing < 2500 g. However, in the unaware group, 56.7% had still birth, and preterm delivery was observed in 46.7% pregnancies. Totally, 96 pregnancies had low birth babies weighing < 2500 g. Among systemic review of pregnancy outcomes in CKD, it was observed that the incidence of premature birth in women with CKD was consistently higher along with the risk of IUGR observed to be five times higher. The risk of neonatal mortality was fivefold higher and a ninefold risk of still births. Studies observed a fivefold increase in risk of low birth weight (25).

Worsening of renal failure during and following pregnancy was observed among all stages of CKD, but was more evident when GFR < 60 ml/min. This decline in GFR was much less as compared to the unaware population with no proper management for CKD. In the aware group, worsening of GFR was observed among 30% patients, while it was 39.7% in the unaware group. 6.9% became ESRD after pregnancy in aware group, while 16.8% became so in the unaware group focusing the need for careful evaluation and management of CKD among pregnant females. Average time to dialysis from the last pregnancy was faster among the unaware population. Those females who were having presumably glomerular illness faired poorly than ones with interstitial illness. This is evident from the literature wherein approximately 25–38% of pregnant women with moderate CKD show decline in renal function evident by an increase in S creatinine during pregnancy [7] which may persist in one-third of the women for 6 months postpartum and in 10% of the total cohort reach ESRD. Those women with a more severe renal functional impairment (GFR < 40 mL/min/1.73 m^2) and proteinuria exceeding 1 g/day had poorer outcomes, the combination resulting in worse outcomes than either factor alone [12]. This was evident in our study population, 48.8% had progressed to stages $3 + 4$ in the aware group and 48.9% in the unaware population with a larger percentage progressing to ESRD in the unaware population. There was decline in GFR even among those in stage 1 or 2, yet it was more evident in the unaware group, suggesting that judicious monitoring of pregnancy is essential among these females. Complications are even higher in women with more severe kidney disease at conception. Our observation was supported by the literature evidences that 82% of women with severe CKD had chronic hypertension and 64% developed preeclampsia [7, 12–15] with significant deterioration in maternal kidney function in over 25% of women (24). The risk of accelerated progression to ESRD was highest when serum creatinine was found to be greater than 1.9 mg/dl at the beginning of the pregnancy [7]. In our study population, preeclampsia was an important complication of pregnancy evident in both study population though higher in unaware group, i.e., 37.5% pregnancies.

Hence, it is essential to screen all ladies before pregnancy for proteinuria as well as renal dysfunction to avoid maternal and fetal complication. In our study population, those pregnancies where ante-natal check-ups were available and were intensively monitored by the obstetrician with multidisciplinary support of a nephrologist and neonatologist faired better than unmonitored pregnancies. Higher preterm and low birth babies were born to females unaware about their renal illness as compared to better monitored female.

Conclusions

Chronic kidney disease is often clinically and biochemically silent until renal impairment is advanced. Some women are found to have chronic kidney disease for the first time during pregnancy. Around 20% of women who develop early preeclampsia ($\leq$ 30-week gestation), especially those with heavy proteinuria, have previously unrecognized chronic kidney disease. Hence, pregnancy can be a check point in females to pick up for any evidence

of renal dysfunction and appropriately managed for better maternal and fetal outcome.

Compliance with ethical standards

Conflict of interest There is no conflict of interest between any of the authors.

Ethical approval The paper is as per ethical standards approved by our own ethical committee in our institute.

Research involving human patients/animals rights This research focussed on the human patients.

Informed consent The informed consent was obtained from all the patients enrolled in the study.

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