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Neonatal renal immaturity, proteinuria and glomerular filtration rate: A neglected close interknit trio

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Abstract

Objective: To assess the urinary total protein excretion in neonates at different gestational ages. To calculate the Glomerular filtration rate of neonates at different gestational ages.

Methods: Cross sectional study was conducted at tertiary hospital in India. We randomly selected 175 normal newborns of different gestational ages. Systemic random spot second urine samples of normal newborns were selected (urine which baby had passed for first time after birth was not used for sampling. Samples were used to estimate urinary proteins (total)(mg/dl), urine albumin(mg/dl) and urinary creatinine(mg/dl). Urine Albumin Creatinine ratio (mg/gm) was calculated using above variables. Similarly cord blood at birth and blood sample at 24 hours of life were taken to estimate serum creatinine. This was used to calculate eGFR from cord blood and blood samples at 24 hours of life respectively.

Results: Minimum and maximum eGFR was 18.3 and 37.1 ml/min/ 1.73m^2, serum creatinine values were ranging from 0.7 to 0.8 mg/dl. Spot urine total protein values were ranging between 10-30 mg/dl. Spot urine microalbumin values ranged from 0.9 – 9.1mg/dl.

Conclusion: eGFR of newborns in our sample whose gestational age varied from 28 to 41 weeks of gestation ranged from 19.6 – 37.1 ml/1.73m^2/min, this clearly shows that all neonates behave like patients of CKD stage III / IV in terms of functional capacity of their kidney and hence extreme care should be taken while handling their fluids, electrolytes and acid base status and during administering nephrotoxic drugs. All newborns have proteinuria which is primarily tubular in origin due to tubular immaturity.

Introduction

Human urine consists primarily of water and waste by products which are formed as a result of human body metabolism. Apart from water and waste by products other substances such as chemicals are also excreted through the urine. Of all the substances excreted through the urine, protein is the most important and clinically relevant.[(1)]*AbnormalProteinuria* is defined as urine protein excretion which is greater than 100mg/m^2 of body surface area / 24 hrs , which is calculated from a sample of timed urine collection, or from a ratio of urine protein (mg/dl)/ urine creatinine (mg/dl), which is greater than 0.5 and it is calculated from a single spot urine sample. The normal urinary protein excretion in a premature infant is estimated to be 29mg/24hrs and in a full term infant it is estimated to be 32mg/24hrs.Most of the healthy children excrete a small amount of protein in their urine, which represents the so called physiological proteinuria. When corrected for body surface area it is noticed that the excretion is highest in newborn infants which decreases with age.As we know that in

newborns the nephron maturity is not completed at birth, newborns in the early neonatal period ranging from day 1 of life to day 7 of life may develop acute kidney injury due to functional causes such as decreased renal perfusion or due to intrinsic causes such as an acute insult or it can be due obstructive cause such as an anatomic urinary tract obstruction.So urinary protein estimation is important for establishing the diagnosis, follow up and the prognosis of the disease.(2)

Glomerular filtration rate is the volume of fluid which is filtered from the renal glomerular capillaries into the bowman's capsule per unit time. The absolute glomerular filtration rate and the relative glomerular filtration rate in the newborns is much lower than that of older children and adults. Maturation of the neonatal glomerular filtration rate depends upon the development of the renal blood flow. After delivery there is a marked increase in the systemic blood pressure and a decrease in the renal vascular resistance which results in increased renal blood flow which further leads to increase in the glomerular filtration rate. In neonates at day 1 of life, glomerular filtration rate may be as low as 15ml/1.73m^2/min.Proteinuria in neonatal period is not much-discussed topic but its clinical implications in neonates suffering from AKI are quite debatable. It usually creates confusion when assessing improvement in renal function in neonates with AKI when normally their eGFR is < 30 ml/min/1.73m^2. Various renal biochemical parameters vary with gestational age, thus further adding to the confusion. So, urinary protein estimation is important for establishing the diagnosis, follow up and the prognosis of the disease.

Materials and methods

Cross sectional study was conducted at tertiary hospital in India. We randomly selected 175 normal newborns of different gestational ages.Systemic random spot second urine samples of normal newborns are selected (urine which baby had passed for first time after birth was not used for sampling) in the study population from the babies delivered at department of Obstetrics and Gynecology at a tertiary hospital in India and the sample was taken at 24 hours of life by using Pediatric urine collecting bag. Samples were used to estimate urinary proteins (total)(mg/dl), urine albumin(mg/dl) and urinary creatinine(mg/dl). Urine Albumin Creatinine ratio (mg/gm) was calculated using above variables. Similarly cord blood at birth and blood sample at 24 hours of life were taken to estimate serum creatinine. This was used to calculate eGFR from cord blood and blood samples at 24 hours of life respectively.

Exclusion Criteria

1. Newborns whose Apgar score <7,
2. Who were large for date,
3. Whose cord blood serum creatinine was >1mg/dl and suffering co-morbid illness.
4. Newborns whose mothers were suffering from any illness during antenatal period

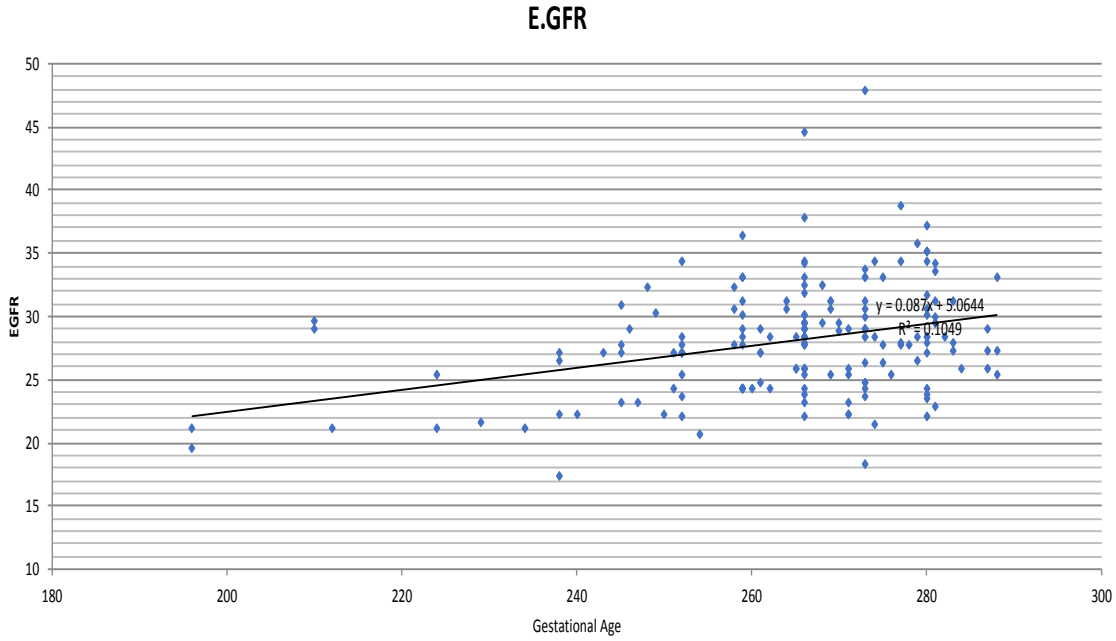
Tests used

1. Urine total proteins were estimated using Pyrocatechol Violet method,
2. Urine creatinine was estimated using Enzymatic Amidohydrolase method
3. Urine albumin was estimated using Immunoturbidometric method
4. Serum creatinine was estimated Enzymatic Amidohydrolase method.
5. All tests were assayed on Vitrous 4600 Analyser
6. eGFR was calculated using modified Schwartz formula

Results

Table 1: Depicts the gestational age bands of sample newborns and their eGFR values distributed according to their gestational age bands

GESTATIONAL AGE (days)	N	MIN eGFR	AVG eGFR	MAX eGFR	Pearson correlation and coefficient(r)
196 - 210	4	19.6	24.8	28.9	
210 - 224	3	21	22.5	25.3	
224 - 238	6	17.4	22.6	27.1	
238 - 252	13	22.2	26.6	32.3	0.324
252 - 266	39	20.6	27.5	36.4	
266 - 280	77	18.3	28.9	47.9	
> 280	33	22	29	37.1	



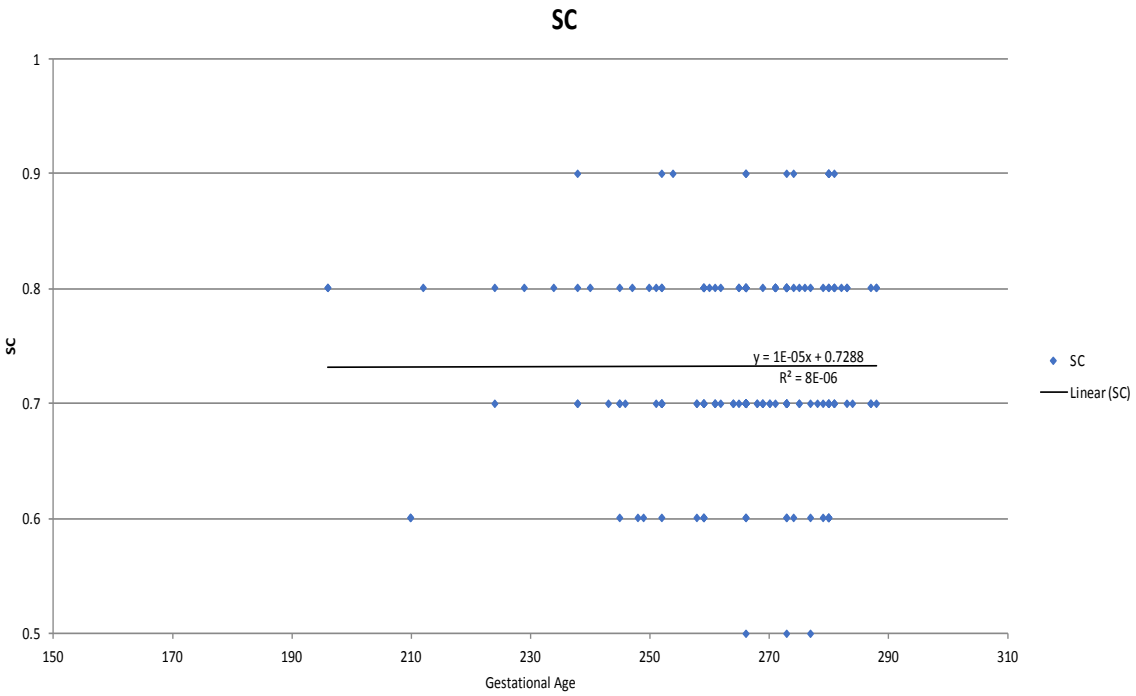
The figure 1: depicts the relationship between eGFR value of newborns with their gestational age at 24 hours of life

Table 1 depicts the gestational age bands of sample newborns and their eGFR values distributed according to the gestational age bands.It can be seen that the eGFR was highest in >280 days of life with average value of 29 ml/1.73m^2/min and the minimum value being 22 ml/1.73m^2/min and the maximum value of 37.1 ml/1.73m^2/min respectively.The minimum value of eGFR was seen at 210 - 224 days of life with the eGFR value being 22.5 ml/1.73m^2/min. The average of eGFR at 196 – 210, 224 – 238, 238 – 252, 252 – 266, 266 – 280 days of life was 24.8ml/1.73m^2/min, 22.68 ml/1.73m^2/min, 26.68 ml/1.73m^2/ min, 27.58 ml/1.73m^2/min, 28.98 ml/1.73m^2/min respectively.

The figure.1 depicts the relationship between eGFRvalues of newborns with their gestational age at 24 hours of life.It was found that eGFR has a positive correlation with the gestational age as the Pearson coefficient is 0.324. As the gestation age will increase the eGFR will increase by 0.324.

Table 2 shows the gestational age bands of sample newborns and their serum creatinine values distributed according to their gestational age bands.

Gestational age (days)	N	MIN SC	AVF SC	MAX SC	Pearson correlation and coefficient (r)
196 - 210	4	0.6	0.7	0.8	0.003
210 - 224	3	0.7	0.7	0.8	
224 - 238	6	0.7	0.8	0.9	
238 - 252	13	0.6	0.7	0.8	
252 - 266	39	0.6	0.7	0.9	
266 - 280	77	0.5	0.7	0.9	
> 280	33	0.6	0.7	0.9	

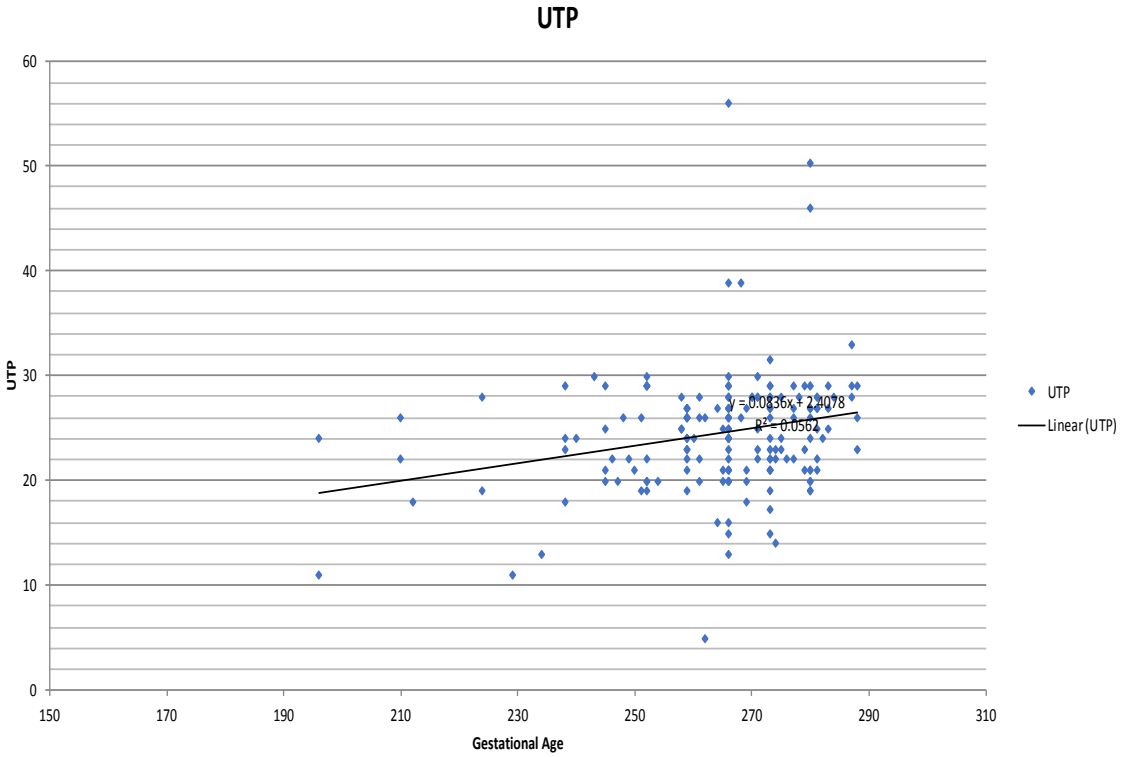


The figure 2: illustrates the relationship between serum creatininevalue of newborns with their gestational age at 24 hours of life.

Table 2 shows the gestational age bands of sample newborns and their serum creatinine values distributed according to the gestational age bands.It can be seen that the serum creatinine was highest in 224 -238 days of life with average serum creatinine value of 0.8 mg/dl and the minimum and maximum serum creatinine value being 0.7 mg/dl and 0.9 mg/dl respectively.The average serum creatinine in all the other gestational ages was 0.7 mg/dl.
The figure 2illustrates the relationship between serum creatinine values of newborns with their gestational age at 24 hours of life.There is a positive correlation between serum creatinine and gestational age of newborns as the Pearson coefficient was 0.003.Hence with increase in gestational serum creatinine will increase by 0.003.

Table 3: Shows the gestational age bands of sample newborns and their urine total protein values distributed according to their gestational age bands

gestational age (days)	N	MIN UTP	AVG UTP	MAX UTP	Pearson correlation and coefficient (r)
196 - 210	4	22	20.7	26	0.237
210 - 224	3	18	21.6	28	
224 - 238	6	11	19.6	29	
238 - 252	13	19	23.4	30	
252 - 266	39	5	23.7	30	
266 - 280	77	13	24.8	56	
> 280	33	19	26.7	50.3	



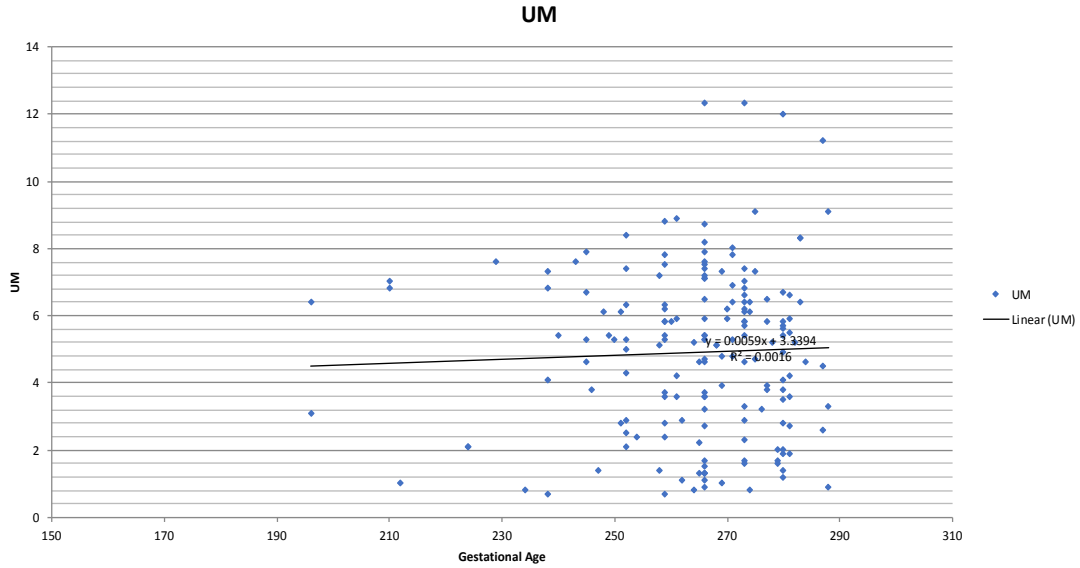
The figure 3: Shows the relationship between urine total protein value of newborns with their gestational age at 24 hours of life

Table 3 depicts the gestational age bands of sample newborns and their urine total protein values distributed according to the gestational age bands.It can be seen that the urine total protein was highest in >280 days of life with the average urine total protein value of 26.7 mg/dl with the minimum and maximum values being 19 mg/dl and 50 mg/dl respectively.The minimum value of urine total protein was seen at 224-238 days of life with the urine total protein value being 19.6 mg/dl.The average urine total protein values at 196- 210, 210 – 224,238-252, 252 – 266,266 – 280 days of life was 20.7 mg/dl, 21.6 mg/dl, 23.4 mg/dl, 23.7 mg/dl, 24.8 mg/dl respectively.

The figure 3 shows the relationship between urine total protein values of newborns with their gestational age at 24 hours of life.It was found that there is a positive correlation between the urine total proteins of newborns and their gestational age as the Pearson coefficient was 0.237.Therefore with increase in the gestational age the urine total protein will increase by 0.237.

Table 4: shows the gestational age bands of sample newborns and their urine microalbumin values distributed according to their gestational age bands.

gestational age (days)	N	MIN UM	AVG UM	MAX UM	Pearson correlation and coefficient (r)
196 - 210	4	3.1	5.8	6.8	0.40
210 - 224	3	1	1.7	2.1	
224 - 238	6	0.7	4.55	7.6	
238 - 252	13	1.4	5.2	7.9	
252 - 266	39	0.7	4.5	8.9	
266 - 280	77	0.8	5.1	12.3	
> 280	33	0.9	4.8	12	



The figure 4: Shows the relationship between urine microalbumin value of newborns with their gestational age at 24 hours of life

Table 4 depicts the gestational age bands of sample newborns and their urine microalbumin values distributed according to the gestational age bands.It can be seen that the urine microalbumin was highest in 196 -210 days of life with urine total protein value of 5.8 mg/dl with the minimum and maximum values being 3.1mg/dl and 6.8 mg/dl respectively.The minimum value of urine microalbuminwas seen at 210 – 224 days of life with the urine microalbumin value being 1.7 mg/dl. The average urine microalbumin at 224 – 238, 238 – 252, 252-266, 266 – 280 and at >280 days of life was 4.55 mg/dl, 5.2 mg/dl, 4.5 mg/dl, 5.1 mg/dl, 4.8 mg/dl respectively.

The figure 4 shows the relationship between urine microalbumin value of newborns with their gestational age at 24 hours of life.There is a positive correlation between urine microalbumin of newborns and the gestational age of newborns as the Pearson coefficient was 0.040.It shows that with increase in the gestational age there will be an increase in the urine microalbumin by 0.040.

Discussion

The definitive human kidney arises from two distinct sources. The nephrons are derived from the metanephros and the collecting part of the kidney is derived from a ureteric bud which arises from the lower part of the mesonephric duct. Differentiation of the metanephros starts

at around 5 weeks of gestation, and the first nephrons are formed by 8 weeks of gestation. Nephrogenesis continues up to 34 to 35weeks of gestation. From the completion of nephrogenesis at around 35 weeks of gestation until the birth, the nephrons grow only in size. At birth, juxtamedullary nephrons are more mature than the superficial nephrons. The total number of nephrons ranges from 600,000 to 1.2 million per kidney. Renal pathologies which lead to proteinuria and albuminuria are quite rare in neonates but still neonatal urine contains proteins.

There have been various studies which indicate that the neonatal urine contains higher amounts of protein than expected due to immaturity of nephrons in neonatal kidneys but these studies have various limitations, like these studies are quite old, sample size is small and different gestational ages have not been used, thus it becomes important to assess and establish normal limits of urine protein and urine albumin in normal newborns at different gestational ages. Similarly, estimated glomerular filtration rate in newborns is very different from that of children and adults. It can be said that if we apply adult and paediatrics Chronic Kidney disease(CKD) classification to the neonatal glomerular filtration rate then neonatal kidneys would fall in CKD stage III. Hence it is important to establish the normal limits for the glomerular filtration rate for newborns of different gestational ages.

In the present study we have tried to find out the variation in renal physiology and renal function with changing gestational age. We used the parameters; spot urine total protein (UTP), estimated glomerular filtration rate (eGFR), serum creatinine (SC), cord serum creatinine(CSC) to study this variation.

Table 1 show that minimum and maximum eGFR of newborns in our study sample were 19.6 and 37.1 ml/1.73m^2/min respectively which shows that on applying pediatric CKD classification to neonatal eGFR, they behave as a patient of chronic kidney disease stage II / IV with respect to its renal physiology. We also found that there was a positive correlation between the gestational age and eGFR with (r) value of 0.324 which means that with rise in gestational age the eGFR increases. Therefore, we conclude that although eGFR improves with gestational age but it is always below 40% of the normal. Thus we would like to put forward our suggestions regarding keeping extreme precaution while managing fluid, electrolyte and acid base imbalances in neonates and while administering nephrotoxic drugs.

We analysed the relationship between the gestational age and SC; during this analysis we used serum creatinine values estimated from blood samples drawn at 24th hour of life. Table 2 depicts that the minimum and the maximum observed values of serum creatinine were 0.5 and 0.9 mg/dl respectively but in majority of samples it ranged from 0.7 - 0.8 mg/dl. There was a positive correlation (r = 0.003) between gestational age and SC. This is very negligible value as can be seen from figure 2, the linear relationship between the gestational age and the SC is almost a horizontal line. Thus we can say that the SC estimated at 24 hours of life values did not depend on the gestational age.

Thus, we can conclude that increasing gestational age does not have much effect on SC of neonate. It can also be seen that all the normal newborns, irrespective of gestational age had SC values <0.9 mg/dl. Thus, we can postulate that any value of SC >0.9 mg/dl after birth should be dealt with caution and should be investigated thoroughly.

It was found that although proteinuria (microalbumin, total protein and tubular protein) varies with gestational age and increases proportionally but this does not happen in case of SC, eGFR also shows improvement. This means that on the basis of biochemical analysis, kidneys do not show any maturity (either tubular or glomerular) and kidney function (SC) remain almost static. Even then eGFR improves, this can be explained with the fact that with the increasing gestation the length of the baby increases and thus eGFR (K x Lt(sc) / SC (mg/dl)**)** also shows rise. Hence, improving eGFR with increasing gestational age gives false sense of improving renal maturity.

The total protein content of the body (body stores of protein) increase with gestational age and thus their excretion also increases even when serum creatinine values are almost same at all gestations. This also gives indirect evidence that maturity level of kidney remains same with increasing gestational age.

Conclusion

eGFR of newborns in our sample whose gestational age varied from 28 to 41 weeks of gestation ranged from 19.6 – 37.1 ml/1.73m^2/min. this clearly shows that all neonates behave like patients of CKD stage III / IV in terms of functional capacity of their kidney and hence extreme care should be taken while handling their fluids, electrolytes and acid base status and during administering nephrotoxic drugs.

The minimum and maximum observed serum creatinine values were 0.5 and 0.9 mg/dl respectively. Hence any value of serum creatinine> 0.9 mg/dl irrespective of the gestational age should be investigated thoroughly.

Serum creatinine values remain within a fixed range throughout different gestational periods but eGFR shows improvement with gestational age which is misleading because eGFR uses length of newborn for estimation which increases with age thus increasing eGFR. Hence, Serum creatinine is superior marker of renal function than eGFR in neonates. About 80% of urine protein is tubular protein thus tubular immaturity is much prominent than glomerular immaturity.

Thus overall we found that it is not worth calculating eGFR in neonates and trying to analyse kidney function and physiology using these variables. On the contrary, it is superior to correlate absolute values of serum creatinine, UTP, with gestational age to asses renal maturity and status of renal insufficiency in case of any episode of renal injury.

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