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Serum Creatinine Levels in First Week of Newborn Infant - Influence of Weight And Gestational Age: A Prospective Cohort Study

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I. Introduction

Serum creatinine measurement is most widely used and commonly accepted index of renal function. It is an important and reliable indicator of renal health because its biological reference intervals are relatively constant during the life time of an adult individual without a superimposed renal failure.Daily Approximately 2% of muscle creatine is converted to creatinine. [(1)(2)] Glycine, arginine, and methionine participate in creatine biosynthesis.Glycine and arginine form guanidoacetate in kidney an intermediate in biosynthesis of creatinine. Creatine synthesis is completed by methylation of guanidoacetate by S- adenosyl methionine[(3)(4)].Creatine is converted to creatine phosphate by creatine kinase, a reversible reaction. Creatine by a non-enzymatic, irreversible, spontaneous reaction is converted to creatinine, which is anhydride of creatine .[(4)(5)]

Kidneys remove creatinine from the blood primarily by glomerular filtration and proximal tubular secretion. Little or no tubular reabsorption of creatinine occurs. Renal function can be evaluated by measuring the GFR. As it is not easy to measure the GFR directly, the serum creatinine concentration is often used to assess renal function.[(1)] If the kidney filtration is deficient, creatinine blood levels rise. Therefore, creatinine levels in blood and urine may be used to calculate the creatinine clearance (CrCl), which correlates with the glomerular filtration rate (GFR). Blood creatinine levels may also be used alone to calculate the estimated GFR (eGFR).[(6)(7)] Serum creatinine (SeCr) concentration is the most commonly used glomerular filtration marker in adult persons. It is also used to asses glomerular filtration rate in neonates .[(8)] Glomerular filtration rate is low in fetal and neonatal life. It increases after birth and reaches approximately 20 mL/min/1.73 m^2 at 1 month of age in term and preterm neonates. The methods used to measure glomerular filtration rate in neonates are inulin clearance, creatinine clearance, and serum cystatin C. Serum creatinine or calculated creatinine clearance are the most convenient estimates of GFR, requiring only a single blood sample and urine sample at same time. [(1) (9)] During the first few days of life, the serum creatinine reflects maternal renal function or the maternal creatinine. Serum creatinine is transported across the placenta in a bidirectional manner. Serum creatinine reflects maternal GFR for at least initial 72 hrs.[(10)(8)]

The assessment of renal function is critical for the adjustment of medication dosing and in planning fluid, nutritional and electrolyte support. The measurement and interpretation of renal function in premature neonates is complicated by in utero events, maternal drug exposure , mode of delivery, gestational age, birth weight, postnatal illness severity, renal development and changing muscle mass.[(11)] The serum creatinine in preterm infants can initially increase before it declines to a steady state and does not necessarily represent acute kidney injury[(12)]. Preterm birth is often associated with gestational diseases affecting placental function and/or maternal renal function. Furthermore, some gestational diseases may also affect fetal glomerular development by inducing intrauterine growth restriction.[(13)] However, data on how these values change over time and how they are influenced by gestational age and birth weight are limited. In the light of these facts, the purpose of this study was to evaluate serum creatinine levels in the 1st week of life in newborn infants, in relation to gestational age and birth weight.

II. Aims And Objectives Of The Study

Aim:

1. To evaluate influence of gestational age and birth weight on newborn serum creatinine levels in the first week of life

Objectives:

1. To study the influence of birth weight and gestational age on newborn serum creatinine levels
2. To correlate maternal serum creatinine levels with newborn serum creatinine levels in the first week of life.

III. Review Of Literature

The renal system plays a tremendous role in growth and development of infants and children. The kidney itself also undergoes a maturation process and assists transition from the fetal to the extra uterine environment. Renal function continues to undergo further adaptive changes in the neonatal period. It is important for the clinician caring for neonates to be aware of the expected fluid shifts, electrolyte handling, and renal functional capacity as these "normal" changes will become quite relevant when medical or surgical pathology is present. The preterm neonates are especially vulnerable due to their functionally immature kidneys. Renal function in the preterm neonate is not only immature at birth but there is a significant delay in the renal function to achieve its full capacity.[14]

Renal function is significantly lower in preterm neonates than term neonates according to Mannan MA, Shahidulla M et al., conducted a study on "Postnatal development of renal function in preterm and term neonates". The study also indicates that the maturation of renal function occurs earlier in the term babies than the preterm babies.[15] In 2009 S Iacobelli, F Bonsante et al., conducted a study to investigate maternal and neonatal factors associated with serum creatinine (SeCr) changes in a representative cohort of preterm newborns during their first week of life and concluded that Se Cr peak was inversely correlated to GA in preterm infants born less than 32 weeks of GA. Neonatal rather than maternal morbidity affected Se Cr peak. In hs PDA, Se Cr increase preceded ibuprofen administration.[10]

In 2008, S Thayyil, S Sheik et al., conducted a retrospective cohort study to create reference ranges for plasma creatinine in extremely premature infants and concluded that Gestation and postnatal age based reference charts should be used for interpretation of creatinine values in extremely premature babies. [16] Karel Allegaert,, Brian J.et al ., conducted a study in 2007 to asses Renal Drug Clearance in Preterm Neonates in Relation to Prenatal Growth and observed that renal drug clearance is significantly lower in preterm neonates born SGA than in appropriate-for-gestational-age (AGA) controls.[17] In 2014 Lina Gubhaju, Megan R.et al .,conducted a study to asses renal functional maturation and injury in preterm neonates during the first month of life and observed that Glomerular and tubular function was significantly affected by gestational age at birth, as well as by postnatal age. By postnatal day 28, creatinine clearance remained significantly lower among preterm neonates compared with term infants. Their findings suggest that neonatal renal function is predominantly influenced by renal maturity and there was high capacity for postnatal tubular maturation among preterm neonates. [18]

A case control study in 2005 conducted by L Cataldi, R Leone et al., on possible associations between the development of acute renal failure in preterm newborns and therapeutic interventions(drug treatments) concluded that there is need for careful monitoring of very low birth weight infants and attention to drug treatments, as it is difficult to differentiate between normality and renal failure in the first few days of life.[19] In 2007 Vasileios Giapros, Photeini Papadimitriou et al., conducted a prospective study on effect of intrauterine growth retardation on renal function in the first two months of life and concluded that Preterm SGA infants who had no need of aminoglycoside treatment after birth have similar renal functional maturation than AGA preterm infants at 2 months of life, but preterm SGA infants who received aminoglycosides had impaired glomerular and tubular function at this age.[20]

In 2013 Alexandra Bruel1, Jean-Christophe Rozé et al .,conducted a retrospective study to define the critical creatinine values by gestational age in preterm infants before 33 weeks and concluded that the values greater than critical levels were associated with mortality, and non-optimal neural development outcome at two years .[21] In 2011 MW Walker1, RH Clark et al., conducted a retrospective study to describe the changes in plasma creatinine levels that occur in prematurely born neonates, to better understand the use of the terms 'renal dysfunction' and 'renal failure' among premature neonates, as well as to evaluate the demographic and outcome characteristics associated with renal problems in preterm neonates who have no major congenital anomalies and concluded that renal dysfunction and failure are common diagnoses in extremely premature neonates and there are potentially modifiable factors (vasopressor usage, grade 3 or 4 intraventricular hemorrhage, patent ductus arteriosus, necrotizing enterocolitis and culture positive sepsis)that increase the risk of renal problems.[22]

In 2006, A Auron and MJ Mhanna conducted a study to know about the relationship between gestational age (GA), birth weight (BW) and serum creatinine in very low birth weight (VLBW) infants and postnatal serum creatinine changes and to determine the correlation between GA or BW and serum creatinine in VLBW infants during their first days of life. This study concluded that in VLBW infants serum creatinine decreases significantly during the first days of life; however, in infants younger than 29 weeks GA or smaller than 1000 g BW there is a delay in the decrease of their serum creatinine that extends beyond the first days of life. They also concluded that during the first few days of life and in VLBW infants serum creatinine decreases with advancing GA or BW.[23] David A. Bateman, William Thomas et al., conducted a retrospective study in 2015 on serum creatinine concentration in very-low-birth-weight infants from birth to 34–36 wk postmenstrual age and their results observed in 3 phases, In phase I(initial post natal), s[Cr] increased after birth, then returned slowly to baseline over one week. The duration of phase I and the magnitude of s[Cr] rise decreased with

increasing GA. In phase II (Rapid decline), s [Cr] declined abruptly at a rate that increased with GA. A gradual transition to phase III (equilibrium), a steady-state equilibrium with similar s [Cr] among GA groups, began at approximately 34–36 wk PMA. This study concluded that the reference ranges derived from a sample of infants without risk factors for renal impairment provide a context for quantitative interpretation of s[Cr] trends in VLBW infants. Finally, they constructed gestational age group specific normograms depicting serum creatinine behavior across the three phases.[24]

Glomerular Function in Neonates

Glomerular filtration rate (GFR) is as low as one-third to one-fourth of those of adult values in the neonatal period, especially in preterm neonates. Glomerular filtration rate values depend on gestational age, and therefore, are lower in neonates with lower gestational ages. Glomerular filtration rate increases within the first month of life, and the velocity of this increase is lower in preterm neonates. It is necessary for clinicians to track postnatal changes in GFR and the level of GFR at different gestational ages, so that they can recognize the abnormal changes and diagnose kidney failure.[9]

Glomerular filtration

In the fetus, the placenta maintains the fluid and electrolyte balance and clearance of metabolic wastes; thus, GFR is low, but it increases progressively. Within the last months of gestation, GFR increases in parallel with gestational age until the 36th week of gestation, which is due to an increase in the number and size of nephrons. Thereafter, GFR develops more slowly up to the time of birth. At birth, GFR is still relatively low; measured by inulin clearance at birth, it is almost 20 mL/min/1.73 m2 in term neonates. In term infants, there is a large increase in GFR during the first 2 weeks after birth. All determinants of the single-nephron GFR contribute to this increasing by varying degrees. Increases in systemic blood pressure and consequently hydrostatic pressure of glomeruli, pore size of glomerular capillary wall (as well as glomerular capillary surface area) and ultrafiltration coefficient, and plasma flow rate secondary to increase in caliber of afferent and efferent arterioles and the decrease in these arterioles resistance all play some role in maturational increase in early postnatal GFR[9][25]

Some authors believe that this increase in early postnatal GFR is primarily due to an increase in glomerular capillary surface area. In an experimental study, the mechanisms responsible for changes in GFR were investigated in fetal sheep and lambs. This study showed that the striking increase in GFR (occurring in late fetal life and 2 weeks after birth) is due to a small increase in filtration pressure together with a large increase in the ultrafiltration coefficient. However, GFR doubles during the first 2 weeks of life and reaches almost 50 ± 10 mL/min/1.73 m^2 between 2 and 4 weeks after birth. After the 1st month of life, GFR increases progressively and reaches adult levels between 1 and 2 years of life. [9]

Glomerular filtration rate is low in preterm infants at birth and varies by the gestational age. In these neonates, postnatal GFR develops slowly until 34 to 36 weeks of gestation. Thereafter, GFR increases rapidly, like postnatal GFR in term neonates. In a study of 41 preterm neonates with gestational ages from 27 to 36 weeks, postnatal increase in GFR was explained in 2 ways: first, an increase in GFR in association with the increment in gestational age and body weight, and second, another increase in GFR due to renal hemodynamic changes without dependency on gestational age and body weight. Thus, the rapid increase in GFR occurs in preterm infants in a relatively later time. Consequently, doubling GFR occurs later and at the 3rd to 4th week after birth or even later in very preterm infants. At 1 month of life GFR reaches 50 mL/min/1.73 m2 in most preterm neonates .[9]

Kidney function assessment

Various methods have been used to measure GFR in neonates. One of these methods is the clearance measurement. Some endogenous and exogenous substances have been used to measure clearance. These substances include inulin, creatinine, iohexol, ethylene diamine tetraacetic acid (EDTA), diethylene triamine penta acetic acid (DTPA), and sodium iothalamate. However, frequent blood sampling, urine collection, and constant infusion of exogenous markers limit their use. In most neonatal intensive care units, GFR is measured using Schwartz formula, which is based on serum creatinine level.[9]

Creatinine

The source of creatinine is creatine and phosphocreatine of muscles, and therefore, it reflects muscle mass of the body. Plasma creatinine is high and almost 1.1 mg/dL at birth because of circulating maternal creatinine. Then, it falls in the 1st week of life, but is still higher than normal at the end of the 1st week. Thereafter, serum creatinine decreases more slowly to reach 0.4 mg/dL at 2 weeks after birth. In preterm infants, serum creatinine first rises at 2 to 4 days of life and then decreases and reaches to 0.4 mg/dL later and mostly at week 2 to 3 postnatal. The tubular reabsorption of creatinine seems to be the cause of continued high plasma

creatinine in these neonates. By maturation of the renal tubules, the total muscle mass of the body, glomerular filtration rate, and tubular secretion determine serum creatinine concentration. [9]

There are several methods to estimate GFR from serum creatinine. Although creatinine-based GFR is not as precise as inulin clearance-based estimates, it is simple, inexpensive, and almost noninvasive. In clinical practice, creatinine clearance (using serum and urine creatinine concentrations) is used to measure GFR; however, its performance requires timely urine collection and is cumbersome especially in neonates. As a result, studies have used equations to estimate GFR by the use of serum creatinine and patient characteristics such as height, weight, gender, and age. Schwartz formula is the most commonly used equation in pediatric age groups, including neonates. Studies with comparison between GFR estimated by creatinine clearance and the values estimated by the Schwartz formula showed significant correlations in both term and preterm infants. In addition, the GFR obtained by the Schwartz formula is correlated with the inulin single-injection technique. In contrast, there is no significant correlation between GFR measured by this formula with those obtained by the standard inulin clearance. The simplicity of the Schwartz formula leads to the use of this method for estimation of GFR in most centers.[9]

Reference values of serum creatinine in Kamineni hospital clinical laboratory:

Biological Reference interval	mg/dl	µmol/ litre
Male	0.6-1.5	54-135
Female	0.5-1.2	45-108
Neonates		
Premature	0.29-1.04	26.1-93.6
Full term	0.24-0.85	21.6-76.5
Infants	0.20-0.40	18.0-36.0
01-<11 years	0.24-0.70	21.6-63.0
11-<15 years	0.53-0.87	47.7-78.3

IV. Materials And Methods

Study Design:
Prospective cohort study.
Study Site:
Department of Pediatrics, Kamineni Hospitals Ltd., L.B.Nagar, Hyderabad.
Sample size:
All neonates admitted in NICU both preterm and term neonates who fulfill the inclusion criteria during the study period are included.
Inclusion criteria:
All neonates born between 28 and 42 weeks gestational age admitted in NICU at this hospital during a period of 2 years were considered eligible for the study.

Exclusion criteria:
1. Hemodynamically unstable neonates
2 Oliguria
3. Hypotension
4. Culture positive sepsis
5. Sympathetic amines in use.
6. Babies with renal and urinary tract anomalies.
7. Babies with congenital heart disease.
8. Perinatal asphyxia.
9. Babies requiring mechanical ventilator support.
10. Necrotizing enterocolitis
11. Hemodynamically significant patient ductus arteriousus (HsPDA)

From May 2014 to April 2016.

V. Methodology

This prospective cohort study was performed at the Department of Pediatrics, Kamineni Hospital, Hyderabad, which is a tertiary perinatal center. Recruitment of babies for this study was limited to babies admitted to the Neonatal intensive care unit. The study commenced in May 2014, and the recruitment period lasted for 24 months. This study is approved by the ethical committee, Kamineni Hospital, LB Nagar, Hyderabad and mothers who give signed informed consent.

Infants Were Divided Into Three Groups, According To Their Gestational Age:
Group 1, very preterm newborn infants with gestational age of 28 to 32 wks
Group 2, preterm newborn infants with gestational age of 33 to 37 wks
Group 3, term newborn infants with gestational age of 38 to 42 wks

Plasma creatinine levels were collected for all newborn infants B/W 28-42 weeks gestation on Days 0, 3, 5, and 7 admitted to neonatal intensive care unit during study period. Creatinine levels were measured by modified kinetic Jaffe reaction.

VI. Statistical Analysis

The data is entered and analyzed in MS Excel 2007. Statistical analysis was performed using SPSS 17. The data were examined for normality of distribution. Repeated measure analysis of variance (ANOVA) was used to examine the creatinine levels at various gestation categories, birth weight and postnatal ages. The correlation between continuous variables was examined by Pearson correlation coefficient. The categorical variables are summarized by proportions and the continuous variables by mean and SD. The data is graphically summarized by bar charts, tables and pie diagrams.

VII. Observations And Results

During the study period, 1800 newborn infants were admitted to our NICU. 12.1% percent (218/1800) were eligible for the study. So the study population included 218 infants. The demographics of the 218 infants are summarized in Table 1.

Characteristics

Table 1 Characteristics of 218 infants admitted in NICU according to gestational age

Gestational age	28-32wks	33-37wks	38-42wks
Number of infants	53	101	64
Male :female	1.2:1	1.3:1	1.6:1
GA(WKS)(mean)	30.5±0.6	35.0±1	38.8±0.8
Birth weight(gms)(mean)	1133±73	1843±377	2631±665
Mean maternal serum creatinine(mg/dl)	0.79±0.04	0.71±0.06	0.66±0.07
APGAR SCORE AT 1 MIN	5.0	6.0	7.0
APGAR SCORE AT 5 MIN	7.0	8.0	8.0

The gestational ages of three groups of babies were 30.5±0.6, 35.0±1 and 38.8±0.8 weeks respectively. Mean weight of babies was 1133±73 gm (28-32wks), 1843±377gm (33-37wks) and 38-42wks was 2631±665 gm respectively.

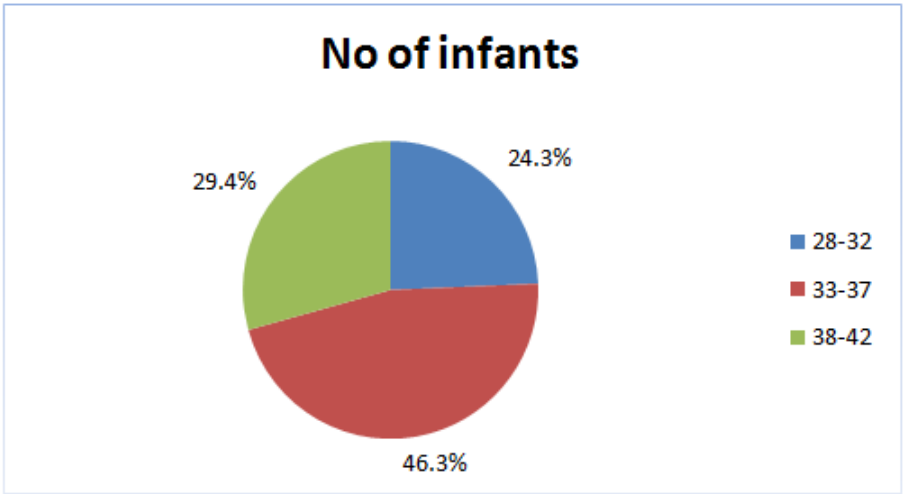
Table 2 Characteristics of 218 infants admitted in NICU according to birth weight Characteristics

Birth weight	<1.5kg	1.5-2.5kg	>2.5kg
Number of infants	74	108	36
Male :female	1.6:1	1.3:1	1.1:1
GA(WKS)(mean)	31.4 ±1.7	36.4±1.9	38.0±1.4
Birth weight(gms)(mean)	1207±149	2005±271	3019±368
Mean maternal serum creatinine(mg/dl)	0.78±0.05	0.70±0.07	0.64±0.06
APGAR SCORE AT 1 MIN	5.0	6.0	7.0
APGAR SCORE AT 5 MIN	8.o	8.0	8.0

The mean gestational ages of three groups of babies were 31.4±1.7, 36.4±1.9 and 38.0±1.4 weeks respectively. Mean weight of babies was 1207±149 gm(<1.5kg),2005±271gm(1.5-2.5kg) and >2.5kg was 3019±368 gm respectively.

Table 3 Distribution of study population according to GA Distribution of study population according to GA

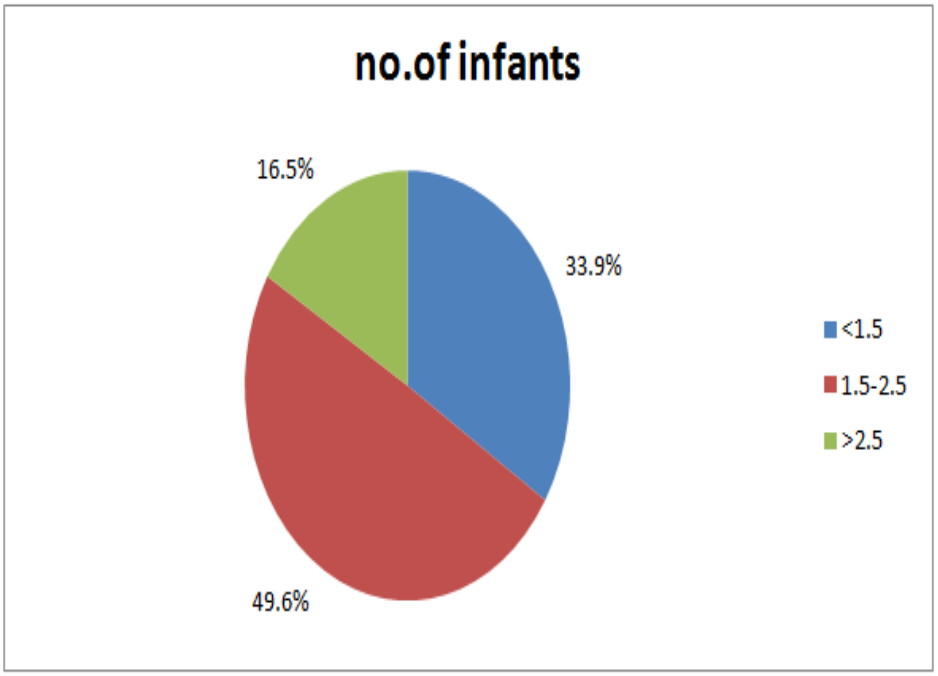
Gestational age(GA)	Number of infants	percentage
28-32wks	53	24.3%
33-37wks	101	46.3%
38-42wks	64	29.4%



Percentage of infants in three groups was 24.3% (28-32wks), 46.3% (33-37wks), 29.4% (38-42wks) respectively.

Table 4 Distribution of study population according to Birth weight

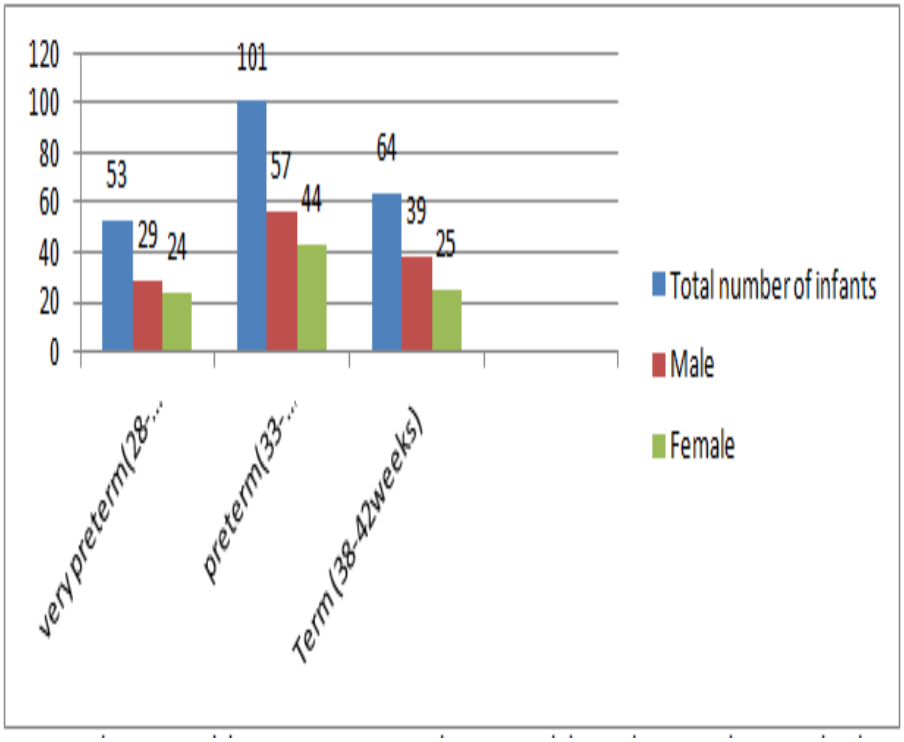
Birth weight(B.W)	Number of infants	percentage
<1.5kgs	74	33.9%
1.5-2.5kgs	108	49.6%
>2.5kgs	36	16.5%



Percentage of infants in three groups was 33.9% (<1.5kgs),49.6%(1.5-2.5kgs),16.5%(>2.5kgs) respectively.

Table 5 Distribution of study population according to gender

	Very preterm (28-32weeks)	Preterm (33-37weeks)	Term (38-42weeks)
Total no of neonates	53	101	64
Male	29	57	39
Female	24	44	25
Ratio	1.20:1	1.30:1	1.56:1



Mean maternal serum creatinine versus mean neonatal serum creatinine on day 0 at various gestational ages

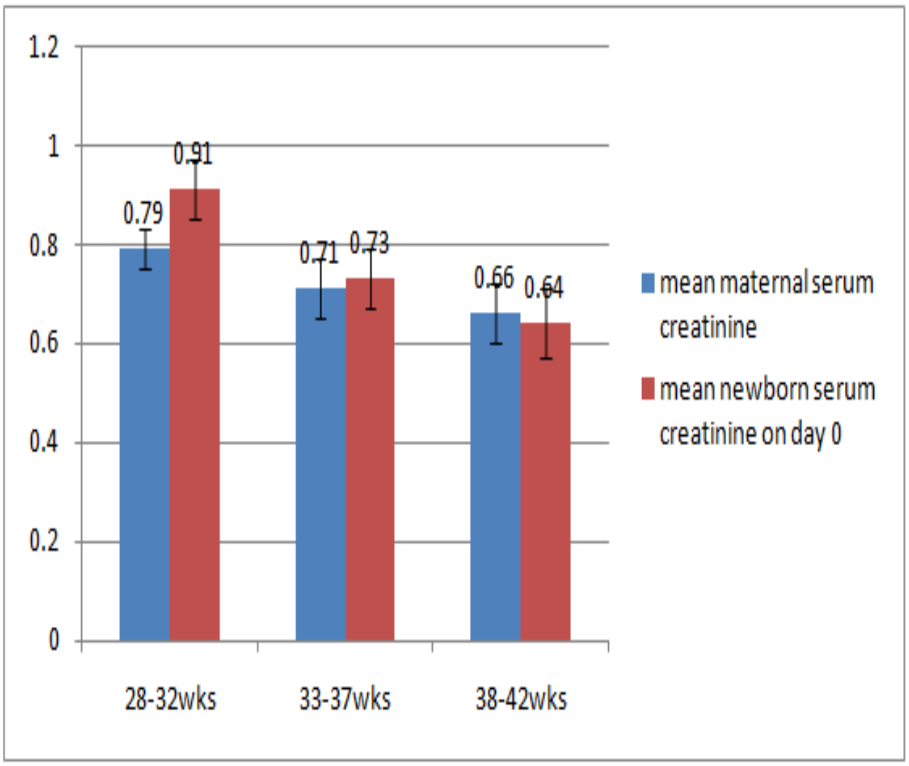


Figure 1 Mean maternal serum creatinine versus mean neonatal serum creatinine on day 0 at various gestational ages

Mean maternal serum creatinine in very preterm, preterm and term groups is 0.79±0.04, 0.71±0.06 and 0.66±0.07mg/dl respectively. Mean neonatal serum creatinine on day 0 in very preterm, preterm and term groups is 0.91±0.06, 0.73±0.06 and 0.64±0.06mg/dl respectively. Mean maternal serum creatinine versus mean neonatal serum creatinine on day 3 at various gestational ages

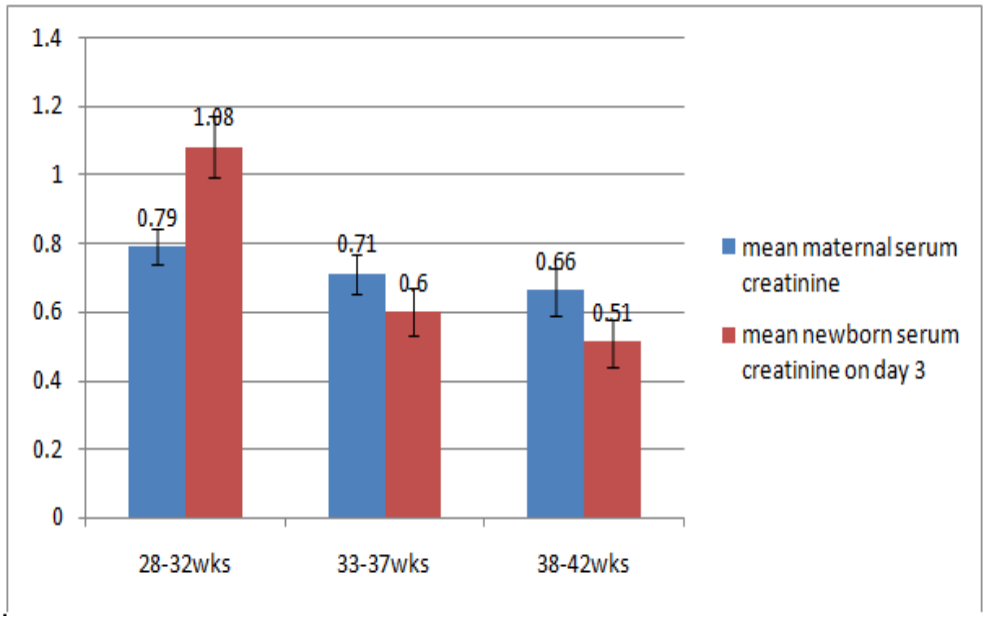


Figure 2 Mean maternal serum creatinine versus mean neonatal serum creatinine on day 3 at various gestational ages

Mean maternal serum creatinine in very preterm, preterm and term groups is 0.79±0.04, 0.71±0.06 and 0.66±0.07mg/dl respectively. Mean neonatal serum creatinine on day 3 in very preterm, preterm and term groups is 1.08±0.09, 0.60±0.07 and 0.51±0.07mg/dl respectively.

Mean maternal serum creatinine versus mean neonatal serum creatinine on day 5 at various gestational ages

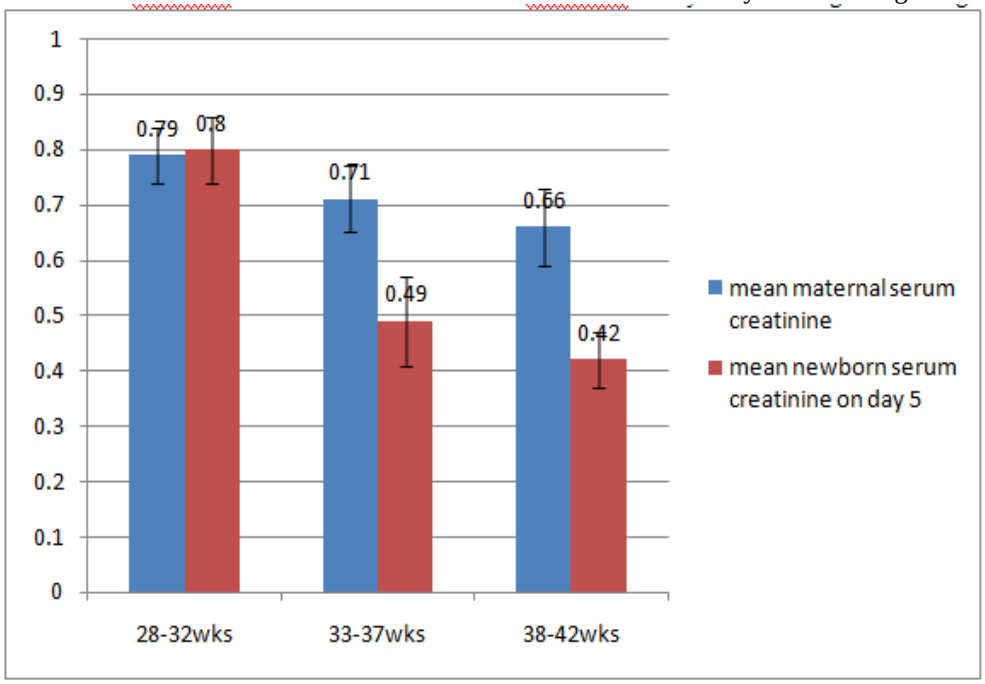


Figure 3 Mean maternal serum creatinine versus mean neonatal serum creatinine on day 5 at various gestational ages

Mean maternal serum creatinine in very preterm, preterm and term groups is 0.79±0.04, 0.71±0.06 and 0.66±0.07mg/dl respectively. Mean neonatal serum creatinine on day 5 in very preterm, preterm and term groups is 0.80±0.06, 0.49±0.08 and 0.42±0.05mg/dl respectively.

Mean maternal serum creatinine versus mean neonatal serum creatinine on day 7 at various gestational ages

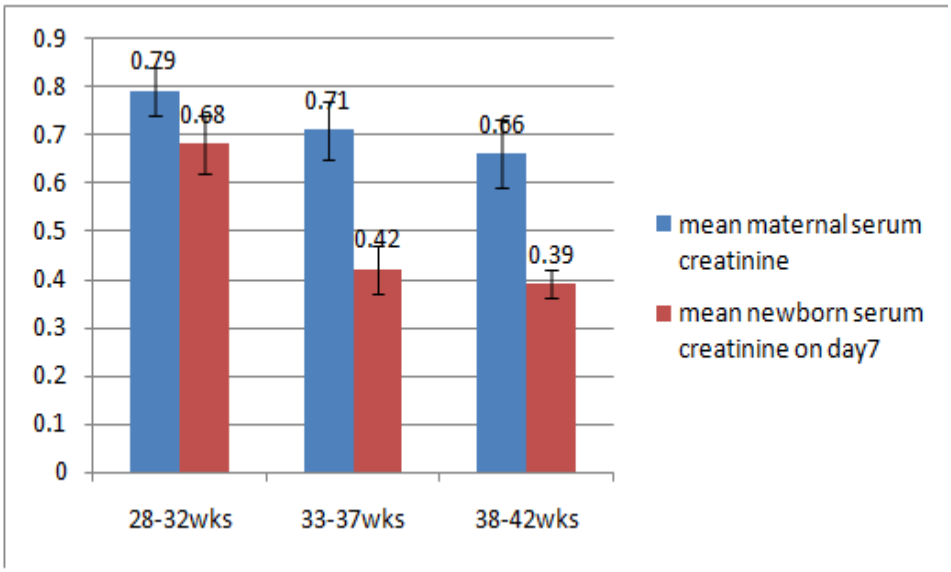


Figure 4 Mean maternal serum creatinine versus mean neonatal serum creatinine on day 7 at various gestational ages

Mean maternal serum creatinine in very preterm, preterm and term groups is 0.79±0.04, 0.71±0.06 and 0.66±0.07mg/dl respectively. Mean neonatal serum creatinine on day 7 in very preterm, preterm and term groups is 0.68±0.06, 0.42±0.05 and 0.39±0.03mg/dl respectively.

Mean maternal serum creatinine versus mean neonatal serum creatinine on day 0 in relation to birth weight.

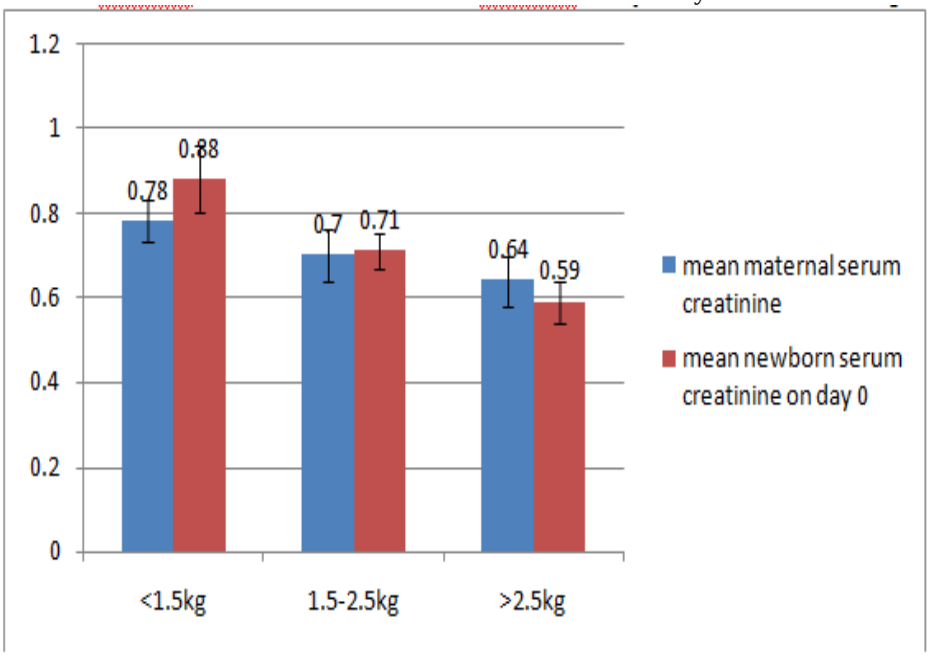


Figure 5 Mean maternal serum creatinine versus mean neonatal serum creatinine on day 0 in relation to birth weight

Mean maternal serum creatinine in very low birth weight, low birth weight and normal birth weight groups are 0.78±0.05, 0.70±0.07 and 0.64±0.06mg/dl respectively. Mean neonatal serum creatinine on day 0 in very low birth weight, low birth weight and normal birth weight groups are 0.88±0.08,0.71±0.04 and 0.59±0.05mg/dl respectively.

Mean maternal serum creatinine versus mean neonatal serum creatinine on day 3 in relation to birth weight

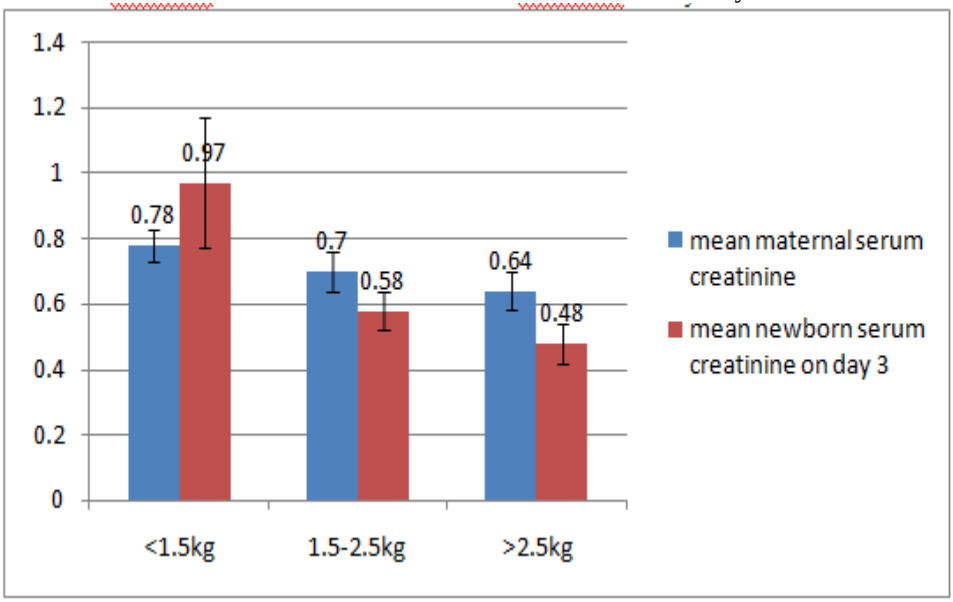


Figure 6 Mean maternal serum creatinine versus mean neonatal serum creatinine on day 3 in relation to birth weight

Mean maternal serum creatinine in very low birth weight, low birth weight and normal birth weight groups are 0.78±0.05, 0.70±0.07 and 0.64±0.06mg/dl respectively. Mean neonatal serum creatinine on day 3 in very low birth weight, low birth weight and normal birth weight groups are 0.97±0.20, 0.58±0.06 and 0.48±0.06mg/dl respectively.

Mean maternal serum creatinine versus mean neonatal serum creatinine on day 5 in relation to birth weight

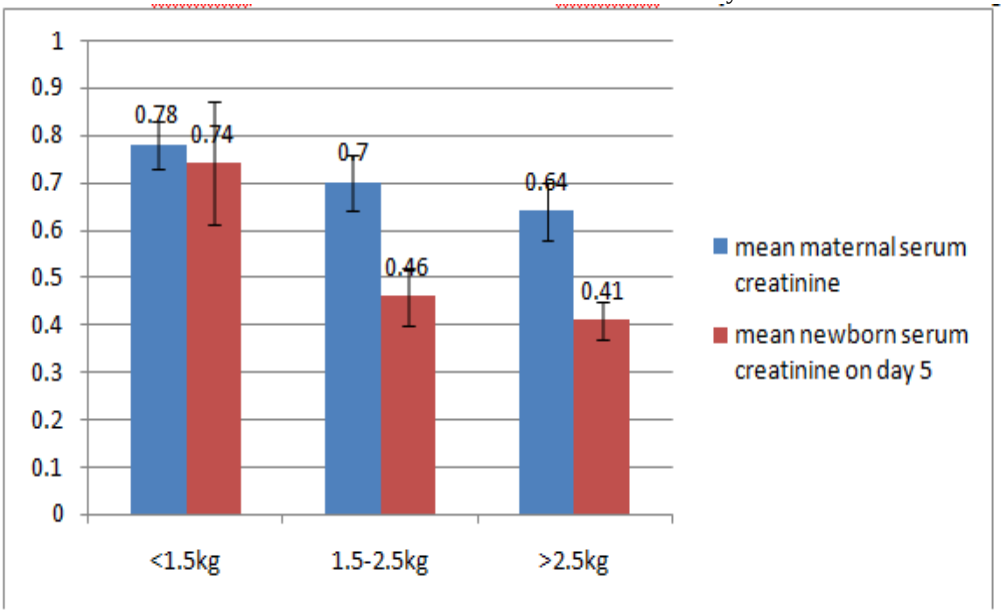


Figure 7 Mean maternal serum creatinine versus mean neonatal serum creatinine on day 5 in relation to birth weight

Mean maternal serum creatinine in very low birth weight, low birth weight and normal birth weight groups are 0.78±0.05, 0.70±0.07 and 0.64±0.06mg/dl respectively. Mean neonatal serum creatinine on day 5 in very low birth weight, low birth weight and normal birth weight groups are 0.74±0.13, 0.46±0.06 and 0.41±0.04mg/dl respectively.

Mean maternal serum creatinine versus mean neonatal serum creatinine on day 7 in relation to birth weight

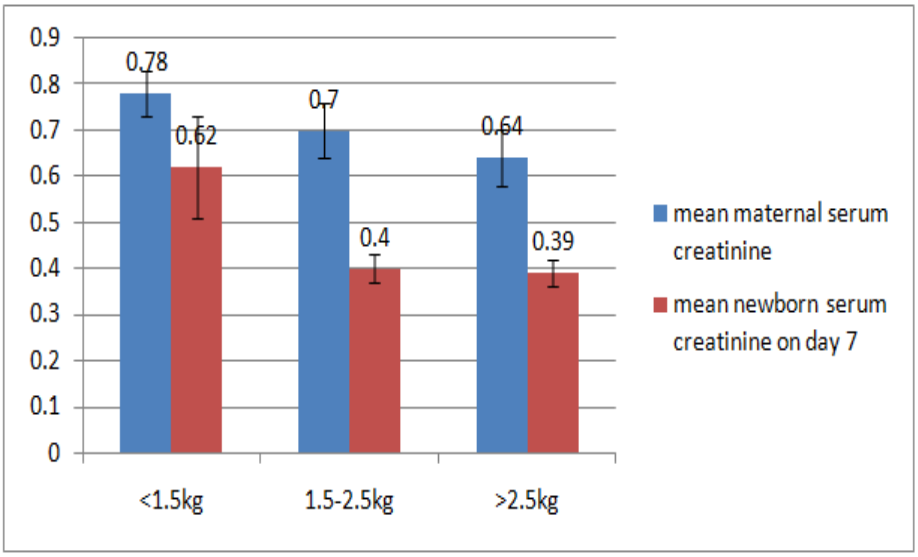


Figure 8 Mean maternal serum creatinine versus mean neonatal serum creatinine on day 7 in relation to birth weight

Mean maternal serum creatinine in very low birth weight, low birth weight and normal birth weight groups are 0.78±0.05, 0.70±0.07 and 0.64±0.06mg/dl respectively. Mean neonatal serum creatinine on day 7 in very low birth weight, low birth weight and normal birth weight groups are 0.62±0.11, 0.40±0.03 and 0.39±0.03mg/dl respectively.

Creatinine values and trends in various gestational ages

Table 6 Shows the values of creatinine (mg/dl) on day 0, 3, 5 and 7 days of life, as well as the values in each subgroup of the population in relation to gestational age.

G.A	DAY O	DAY 3	DAY 5	DAY7
28-32wks	0.91±0.06	1.08±0.09	0.80±0.06	0.68±0.06
33-37wks	0.73±0.06	0.60±0.07	0.49±0.08	0.42±0.05
38-42wks	0.64±0.06	0.51±0.07	0.42±0.05	0.39±0.03

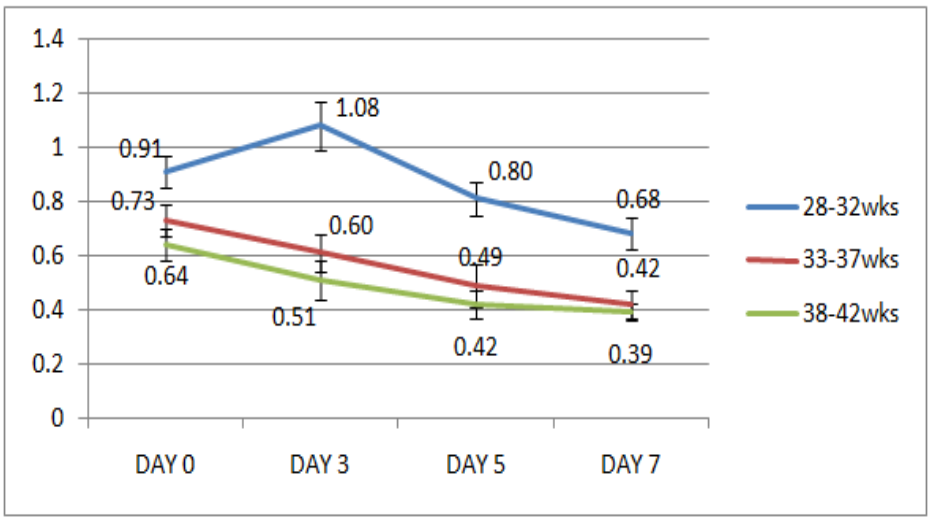


Figure 9 Shows the changes in the values of serum creatinine (mg/dl) in each GA group over time.

The mean serum creatinine of all the three groups decrease from day 0-7 except that in very premature group(28-32wks) where serum creatinine increases from birth to day 3 of life and then subsequently decreases similar to other groups. P value is <0.001 among three groups.

Creatinine values and trends in relation to birth weight

Table 7 Shows the values of Creatinine (mg/dl) on day 0, 3, 5 and 7 of life, as well as the values in each subgroup of the population in relation to BW

B.W	DAY O	DAY 3	DAY 5	DAY7
<1.5kgs	0.88±0.08	0.97±0.20	0.74±0.13	0.62±0.11
1.5-2.5kgss	0.71±0.04	0.58±0.06	0.46±0.06	0.40±0.03
>2.5kgs	0.59±0.05	0.48±0.06	0.41±0.04	0.39±0.03

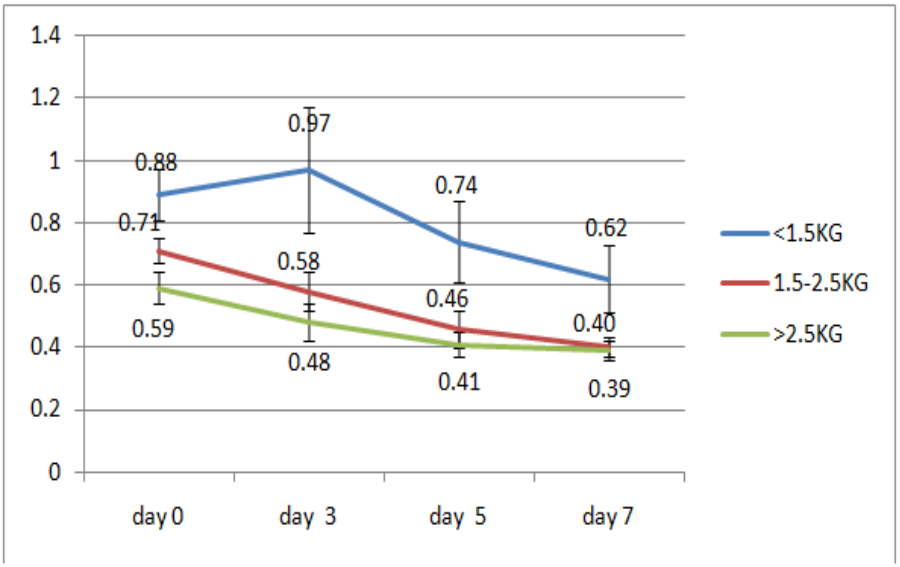


Figure 10 Shows the changes in the values of serum creatinine in each BW group over time

The mean serum creatinine of all the three groups decrease from day0-7 except that in very low birth weight group (<1.5kg) where serum creatinine increases from birth to day 3 of life and then subsequently decreases similar to other groups. P value is <0.001 among three groups.

VIII. Discussion

Serum creatinine measurement is most widely used and commonly accepted index of renal function. The assessment of renal function is critical for the adjustment of medication dosing and in planning fluid, nutritional and electrolyte support. The measurement and interpretation of renal function in premature neonates is complicated by in utero events, maternal drug exposure, mode of delivery, gestational age, birth weight, postnatal illness severity, renal development and changing muscle mass. We measured maternal serum creatinine and newborn serum creatinine levels at different gestational ages and birth weight on days 0,3,5 and 7.The pediatric age group and females have lower serum creatinine than adult population due to lower muscle mass. But contrary to this basic scientific fact, early neonates with insignificant muscle mass have higher serum creatinine. Some times more than maternal serum creatinine.

We enrolled 218 newborn infants in our study. All neonates born between 28 and 42 weeks of gestational age admitted in NICU at this hospital during a period of 2 years (2014-2016) were included in the study. We excluded those babies who are hemodynamically unstable, urine output <1ml/kg/hr, hypotension, culture positive sepsis requiring inotropic support(dopamine and dobutamine etc.),Babies with congenital heart diseases, urinary and renal anomalies, babies requiring ventilator support, and babies with perinatal asphyxia and necrotizing enterocolitis are excluded from our study. Of the 218 newborn infants 53 are very preterm neonates, 101 are preterm neonates, 64 are term neonates. The mean gestational ages of three groups of babies are 30.5±0.6, 35.0±1 and 38.8±0.8 weeks respectively. Mean weight of babies are 1133±73 gm (28-32wks),1843±377gm(33-37wks) and 38-42wks was 2631±665 gm respectively. Male to female ratio is 1.34:1.

Mean maternal serum creatinine in very preterm, preterm and term groups is 0.79±0.04, 0.71±0.06 and 0.66±0.07mg/dl respectively. Mean neonatal serum creatinine on day 0 in very preterm, preterm and term groups is 0.91±0.06, 0.73±0.06 and 0.64±0.06mg/dl respectively. The mean serum creatinine on day 0 in all the three groups (very preterm,preterm and term neonates) was found to be higher than that of the their mean maternal serum creatinine concentrations (fig 1).Mean serum creatinine level is 0.91±0.06mg/dl in very preterm neonates on day 0 of life. While the maternal mean serum creatinine concentration of the very preterm neonates is 0.79±0.04mg/dl. Jean-Pierre Guignard and Alfred Drukker et al., had got similar results and they concluded

that the high plasma creatinine levels of the newborn immediately after birth reflect maternal plasma creatinine levels.[32] Though in all the three groups the neonatal mean serum creatinine concentration was found to be higher than the mean maternal serum creatinine concentrations, the difference is not very stark in the preterm and term neonates. Mannan MA,Shahidulla M et al .,have demonstrated that very preterm neonates have higher plasma creatinine than the mature neonates.[15] So we deduce, higher plasma creatinine levels are indicative of prematurity of the kidneys in very preterm babies.

Mean maternal serum creatinine in very preterm, preterm and term groups is 0.79±0.04, 0.71±0.06 and 0.66±0.07mg/dl respectively. Mean neonatal serum creatinine on day 3 in very preterm, preterm and term groups is 1.08±0.09, 0.60±0.07 and 0.51±0.07mg/dl respectively. (Fig2) Our study results showed that Serum creatinine levels increased after birth on day 3 in very preterm neonates(28-32weeks).So study by S lacobelli,F Bonsante et al., also observed that serum creatinine increases in the first 48 hours in very preterm neonates.[10] This can be probably explained by the reflection of the maternal serum creatinine levels which is not excreted by the immature fetal kidneys. On the other hand, mean serum creatinine on day 3 in preterm and term neonates has drastically reduced from 0.73±0.06 to 0.60±0.07 mg/dL in preterm neonates, and 0.64±0.06 to 0.51±0.07mg/dL in term neonates. This explains that kidneys are much mature in term neonates to handle maternal serum creatinine levels.

Mean maternal serum creatinine in very preterm, preterm and term groups is 0.79±0.04, 0.71±0.06 and 0.66±0.07mg/dl respectively. Mean neonatal serum creatinine on day 5 in very preterm, preterm and term groups is 0.80±0.06, 0.49±0.08 and 0.42±0.05mg/dl respectively. (Fig3). It shows that mean serum creatinine levels in all the three groups shows a decreasing trend .But in very preterm neonates on day 5 mean neonatal serum creatinine levels still higher than the mean maternal serum creatinine levels of that group. Where as in preterm and term neonates mean serum creatinine levels are much lower. This finding reiterates the fact that preterm and term neonates metabolize and eliminate creatinine due to the functionally more mature kidneys.

Mean maternal serum creatinine in very preterm, preterm and term groups is 0.79±0.04, 0.71±0.06 and 0.66±0.07mg/dl respectively. Mean neonatal serum creatinine on day 7 in very preterm, preterm and term groups are 0.68±0.06, 0.42±0.05 and 0.39±0.03mg/dl respectively (Fig4).It shows that mean serum creatinine levels in all the three groups shows a downward trend. In our study mean newborn serum creatinine levels in very preterm neonates are 0.91±0.06, 1.08±0.09, 0.80±0.06, 0.68±0.06 mg/dL on day 0, 3, 5,and 7 respectively. Mean newborn serum creatinine levels in preterm neonates are 0.73±0.06, 0.60±0.07, 0.49±0.08, 0.42±0.05mg/dL on day 0, 3, 5,and 7 respectively. Mean newborn serum creatinine levels in term neonates are 0.64±0.06, 0.51±0.07, 0.42±0.05, 0.39±0.03mg/dL on day 0, 3, 5,and 7 respectively.(Fig9) The results were subjected to a significance test called ANOVA (Analysis of variants) to study the significance between the three-sub-groups of the study. The p value is <0.001 between very preterm neonates and preterm neonates, which is to say that one in a thousand is likely to differ from our observations. This is highly significant. The p value is <0.001 between preterm neonates and term neonates, which is also very significant.

Mean maternal serum creatinine in very low birth weight, low birth weight and normal birth weight groups are 0.78±0.05, 0.70±0.07 and 0.64±0.06mg/dl respectively. Mean neonatal serum creatinine on day 0 in very low birth weight, low birth weight and normal birth weight groups are 0.88±0.08,0.71±0.04 and 0.59±0.05mg/dl respectively.(Fig5)The mean serum creatinine levels on day 0 in all the three groups(very low birth weight, low birth weight and normal birth weight neonates) was found to be higher than that of the their mean maternal serum creatinine concentrations except in normal birth weight neonates in which mean neonatal serum creatinine levels less than mean maternal serum creatinine. (fig5). What is intriguing is neonates with less muscle mass have higher serum creatinine than their mothers with more functional muscle mass. A Auron and MJ Mhanna found that during the first 2 days of life the high level of serum creatinine in low birth weight neonates can be attributed to a combination of maternal serum creatinine levels coupled with immaturity of the glomerular filtration, and an increased tubular reabsorption of creatinine due to a possible back-flow of creatinine across leaky immature tubular and vascular structures.[23]

Mean maternal serum creatinine in very low birth weight, low birth weight and normal birth weight groups are 0.78±0.05, 0.70±0.07 and 0.64±0.06mg/dL respectively. Mean neonatal serum creatinine on day 3 in very low birth weight, low birth weight and normal birth weight groups are 0.97±0.20, 0.58±0.06 and 0.48±0.06mg/dL respectively.(Fig6) Our study results showed Serum creatinine levels increased after birth on day 3 in very low birth weight neonates(<1.5kg).This emphasizes the findings by A Auron and MJ Mhanna .[23] On the other hand, mean serum creatinine on day 3 in low birth weight and normal birth weight neonates has drastically reduced from 0.70 to 0.58 mg/dL in low birth weight neonates, and 0.64 to 0.48mg/dL in normal birth weight neonates. This explains kidneys are in the process of maturation from day 3 onwards in low birth weight and normal birth weight neonates.

Mean maternal serum creatinine in very low birth weight, low birth weight and normal birth weight groups are 0.78±0.05, 0.70±0.07 and 0.64±0.06mg/dL respectively. Mean neonatal serum creatinine on day 5 in very low birth weight, low birth weight and normal birth weight groups are 0.74±0.13, 0.46±0.06 and

0.41±0.04mg/dL respectively. (Fig7). It shows that mean serum creatinine levels in all the three groups shows a decreasing trend .But in very low birth weight neonates on day 5 mean neonatal serum creatinine levels still reflect maternal serum creatinine levels because of immature kidneys. Where as in low birth weight and normal birth weight neonates mean serum creatinine levels are much lower. This finding confirms the fact that low birth weight neonates and normal birth weight neonates excrete creatinine due to the functionally more mature kidneys compared to very low birth weight neonates. Mean maternal serum creatinine in very low birth weight, low birth weight and normal birth weight groups are 0.78±0.05, 0.70±0.07 and 0.64±0.06mg/dL respectively. Mean neonatal serum creatinine on day 7 in very low birth weight, low birth weight and normal birth weight groups are 0.62±0.11, 0.40±0.03 and 0.39±0.03mg/dL respectively.(Fig8).It shows that mean serum creatinine levels in all the three groups shows a downward trend.

In our study mean newborn serum creatinine levels in very low birth weight neonates are 0.88±0.08, 0.97±0.20, 0.74±0.13, 0.62±0.11mg/dL on day 0, 3, 5,and 7 respectively. Mean newborn serum creatinine levels in low birth weight neonates are 0.71±0.04, 0.58±0.06, 0.46±0.06, 0.40±0.03mg/dL on day 0, 3, 5, and 7 respectively. Mean newborn serum creatinine levels in normal birth weight neonates are 0.59±0.05, 0.48±0.06, 0.41±0.04, 0.39±0.03mg/dL on day 0, 3, 5,and 7 respectively.(Fig10) The results were subjected to ANOVA(Analysis of variants) to study the significance between the three-sub-groups of the study. The p value is <0.001 between very low birth weight neonates and low birth weight neonates, which is significant. The p value is <0.001 between low birth weight neonates and normal birth weight neonates, which is significant.

The mean newborn serum creatinine at birth in all the three groups(very preterm, preterm and term neonates) was found to be higher than that of the mean maternal serum creatinine .So maternal serum creatinine concentration is expected to contribute to great portion of the newborn serum creatinine levels at birth(on day 0). In the first days of life, newborn and their mothers have similar levels of serum creatinine. After that, newborn levels decrease especially in preterm and term neonates. From our data, we observed that on day 0 Serum creatinine values among the three groups were high despite the low functional mass of neonates. These values are reflection of the maternal serum creatinine and in addition functionally immature kidneys also contribute to high serum creatinine levels .We also observed that serum creatinine in very preterm neonates and very low birth weight neonates does not fall steadily from birth, but rises in the first 2 days of life, reaching a peak and then falling to equilibrium levels. This trend of the fall was slower compared to preterm and term neonates. In the neonates with lower G.A. (group 1; 28-32 wks), after the more marked initial increase in serum creatinine concentrations, the decrease was much slower, perhaps reflecting a slow gradual progression in glomerular function .

In the present study, there was no statistically significant difference between mean newborn serum creatinine determinations on the 5th and 7th day of life in preterm and term neonates. These findings support that maternal creatinine levels have no influence during first week of life, at least after the fifth day. In full-term newborn infants, maternal and neonate creatinine levels are similar in the first days of life .However, in very preterm newborns, the time of influence of the maternal contribution remains unclear, because renal maturity and chronological age are important factors in improved glomerular filtration rate.

In our study, we emphasized that the selected newborn infants showed absence of renal and urinary tract anomalies, satisfactory hemodynamics and respiration (O2 saturation 92% measured by pulse oximeter), adequate urine output (>1 ml/kg/hr), systolic and diastolic blood pressure above the third percentile adjusted for gestational age,and absence of infections; also they had never received drugs that could possibly have influenced the glomerular filtration rate (aminoglycosides, antiepileptic drugs, theophylline, dobutamine, dopamine,indomethacin, midazolan), in order to exclude some factors that could interfere on our results. We also found that smaller the birth weight , higher the serum creatinine levels and that the high serum creatinine remained elevated for a considerable amount of time especially in very low birth weight infants .

Our study results showed that Serum creatinine levels increased after birth in very premature infants(28-32weeks)reaching a peak around day 3 of life before falling steadily in the manner described by S lacobelli,F Bonsante et al.[10] We have demonstrated that the very preterm infants have a higher peak in serum creatinine and subsequent fall in creatinine occurs later than in full term infant. Serum creatinine concentration reflects the balance between production from creatine stores in muscle and clearance by glomerular filtration. Because preterm infants have a small muscle mass, it would be expected that plasma creatinine concentration would be low if renal clearance was normal.

The rise in creatinine that we have demonstrated suggests there is poor creatinine clearance by the preterm kidney in the first few days of postnatal life. Poor creatinine clearance may be attributable to delayed establishment of normal GFR or attributable to reabsorption of creatinine by the immature tubule. Another possibility is that in the immediate postnatal period creatinine is not fully excreted by the neonatal kidney and that partial reabsorption occurs across the immature tubule.

IX. Conclusion

From our study, we concluded that initial rise in plasma creatinine levels in very preterm newborn infants are clearly not secondary to high maternal creatinine alone. It is also due to premature neonatal kidneys .In short higher serum creatinine in neonates is an indicator of prematurity in the first week of life. Our analysis showed that the period of maternal serum creatinine influence is less than one week of life. However, further investigations are warranted in a large cohort of preterm newborn infants with different gestational ages, which may throw more light on pathophysiology..

It was evident from the present study that the renal function is significantly lower in very preterm neonates than term neonates. The study also indicates that the maturation of renal function occurs earlier in the term babies than the very preterm babies

X. Recommendations

An isolated creatinine determination cannot reveal the glomerular filtration status especially in very preterm neonates. Periodic serum creatinine determinations are indicated to better evaluate the glomerular filtration rate.

XI. Limitations

Exact correlations between serum creatinine levels and different gestational ages remain difficult to analyze, because many variables must be considered, such as maternal diseases such as hypertensive disease of pregnancy, hydration and catabolic status, and increase in muscle mass (per unit of body size). Another limitation to our study is the possibility of the presence of a silent PDA that could have affected renal perfusion and function. We excluded patients with hemodynamically significant PDA and who had an echocardiogram to confirm the diagnosis. We did not have cardiac echocardiograms carried out routinely to exclude patients with silent PDA.

Bibilography

[1]. Nankivell JB. Creatinine clearance and the assessment of renal function. Aust Prescr [Internet]. 2001;24(1):15–7. Available from: http://www.australianprescriber.com/magazine/24/1/15/7

[2]. Clark R V, Walker AC, O'Connor-Semmes RL, Leonard MS, Miller RR, Stimpson S a, et al. Total body skeletal muscle mass: estimation by creatine (methyl-d3) dilution in humans. J Appl Physiol [Internet]. 2014;116(12):1605–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24764133

[3]. Murray RK, Bender DA, Botham K. Harper's Ilustrated Biochemistry. 29th ed. 2012. 689-699 p.

[4]. Wyss M, Kaddurah-Daouk R. Creatine and Creatinine Metabolism. Physiol Rev. 2000;80(3):1107–213.

[5]. Allen PJ. Creatine metabolism and psychiatric disorders: Does creatine supplementation have Therapeutic value ? neurobiorev201203005. 2013;36(5):1442–62.

[6]. Lujambio I, Sottolano M, Luzardo L, Robaina S, Krul N, Thijs L, et al. Estimation of glomerular filtration rate based on serum cystatin c versus creatinine in a uruguayan population. Int J Nephrol. 2014;2014.

[7]. Puzantian H V., Townsend RR. Understanding kidney function assessment: the basics and advances. J Am Assoc Nurse Pract. 2013;25(7):334–41.

[8]. Filler G, Guerrero-Kanan R, Alvarez-Elías AC. Assessment of glomerular filtration rate in the neonate. Curr Opin Pediatr [Internet]. 2016;1. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00008480-900000000-99261

[9]. Otukesh H, Hoseini R, Rahimzadeh N, Hosseini S. Kidney Diseases Glomerular Function in Neonates. 2012;6(3):166–72.

[10]. Iacobelli S, Bonsante F, Ferdinus C, Labenne M, Gouyon J-B. Factors affecting postnatal changes in serum creatinine in preterm infants with gestational age <32 weeks. J Perinatol. 2009;29(3):232–6.

[11]. Cuzzolin L, Fanos V, Pinna B, di Marzio M, Perin M, Tramontozzi P, et al. Postnatal renal function in preterm newborns: A role of diseases, drugs and therapeutic interventions. Pediatr Nephrol. 2006;21(7):931–8.

[12]. Quigley R. Developmental changes in renal function. 2012;24(2):184–90.

[13]. Manalich R, Reyes L, Herrera M, Melendi C, Fundora I. Relationship between weight at birth and the number and size of renal glomeruli in humans: A histomorphometric study. Kidney Int. 2000;58(2):770–3.

[14]. Sulemanji M, Vakili K. Neonatal renal physiology. Semin Pediatr Surg [Internet]. Elsevier; 2013;22(4):195–8. Available from: http://dx.doi.org/10.1053/j.sempedsurg.2013.10.008

[15]. Mannan MA, Shahidulla M, Salam F, Alam MS, Hossain MA, Hossain M. Postnatal development of renal function in preterm and term neonates. Mymensingh Med J [Internet]. 2012;21(1):103–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22314463

[16]. Thayyil S, Sheik S, Kempley ST, Sinha A. A gestation- and postnatal age-based reference chart for assessing renal function in extremely premature infants. J Perinatol. 2008;28(3):226–9.

[17]. Allegaert K, Anderson BJ, Anker JN Van Den, Vanhaesebrouck S, Zegher F De. Renal Drug Clearance in Preterm Neonates : Relation to Prenatal Growth. 2007;284–91.

[18]. Gubhaju L, Sutherland MR, Horne RSC, Medhurst A, Kent AL, Ramsden A, et al. Assessment of renal functional maturation and injury in preterm neonates during the first month of life. 2014;149–58.

[19]. Cataldi L, Leone R, Moretti U, De Mitri B, Fanos V, Ruggeri L, et al. Potential risk factors for the development of acute renal failure in preterm newborn infants: a case-control study. Arch Dis Child Fetal Neonatal Ed. 2005;90(6):F514–9.

[20]. Giapros V, Papadimitriou P, Challa A, Andronikou S. The effect of intrauterine growth retardation on renal function in the first two months of life. 2007;(September 2006):96–103.

[21]. Bruel A, Rozé JC, Flamant C, Simeoni U, Roussey-Kesler G, Allain-Launay E. Critical serum creatinine values in very preterm newborns. PLoS One. 2013;8(12) Walker MW, Clark RH, Spitzer AR. Elevation in plasma creatinine and renal failure in premature neonates without major anomalies: terminology, occurrence and factors associated with increased risk. J Perinatol. 2011;31(3):199–205.

[22]. Mhanna AA and M. Serum creatinine in very low birth weight infants during their first days of life. J Perinatol. 2006;26:755–60.

[23]. Bateman DA, Thomas W, Parravicini E, Polesana E, Locatelli C, Lorenz JM. Serum creatinine concentration in very-low-birth-weight infants from birth to 34-36wk postmenstrual age. 2015;
[24]. Kliegman, Santon SG. Nelson text book of pediatrics. 20 th edit. 2016. 2490-2491 p.
[25]. Sadler T. Langman's medical embryology. 13th ed. Green land,south carolina; 2015. 250-253 p.
[26]. Griffith JR. Anatomy at a Glance. Journal of Pediatric and Adolescent Gynecology. 2003. 49-50 p.
[27]. Hall JE, Guyton AC. Guyton and Hall Textbook of Medical Physiology. 2011. 303-307 p.
[28]. Rade Č, Vlajkovi S. Age related anatomical and functional characteristics Kidney in an Embryo and Fetus. Facta Univ [Internet]. 2005;12(2):61–9. Available from: http://facta.junis.ni.ac.rs/mab/mab200502/mab200502-01n.pdf\nfile:///Users/sofiaaol/Desktop/Library.papers3/Articles/2005/?ukuranovi?/FactaUniversitatis 2005 ?ukuranovi?.pdf\npapers3://publication/uuid/6E9314D6-D5D3-4A89-B25B-E8010DCF22
[29]. Cohen L, Manion L, Morrison K. Research Methods in community medicine. 5 th editi. 2005. 97 p.
[30]. Lifechem-creatinine-LR. MODIFIED JAFFE'S METHOD.
[31]. Guignard JP, Drukker a. Why do newborn infants have a high plasma creatinine? Pediatrics. 1999;103(4):e49.

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