Alpha 1 Acid Glycoprotein as a Marker for Diagnosis of Early Onset Neonatal Sepsis in Fullterm Neonates

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Abstract: Background: Despite improved neonatal care over the past decades, neonatal sepsis remains common and life threatening for newborns admitted to the intensive care units. The WHO estimates that 1 million deaths per year representing 10% of all deaths under 5 years are due to neonatal sepsis. Unfortunately, early diagnosis of neonatal sepsis remains challenging for practitioners as the manifestations are vague and require high index of suspicion. There is no single diagnostic test, which can reliably diagnose sepsis in newborns, therefore many tests and sepsis markers are currently used to diagnose or confirm sepsis. **Aim of Study:** This study was conducted in order to evaluate the role of Alpha 1 acid glycoprotein in the early diagnosis of neonatal sepsis. **Material and Methods:** This study was a prospective case control conducted on 65 fullterm neonates who were admitted to NICU of Suez Canal University hospital from May 2013 to August 2014. Neonates were aged from day 0 to day 7 of life, they were categorized into 3 different groups according to clinical symptoms of sepsis, bacteriological and laboratory results. Group I consisted of 30 newborns with positive blood cultures and other biological tests which suggested infections (confirmed sepsis). Group II consisted of 15 newborns with negative blood cultures but who had two or three clinical signs of sepsis (suspected sepsis). The control group included 20 healthy newborns referred for follow up after delivery in SCU obstetric ward. Alpha 1acid glycoprotein (α-1AGP) and CRP were determined sphectometrically and by rapid agglutination test respectively. **Results:** There was a significant highα-1AGP level for confirmed and suspected sepsis. As well, CRP levels were significantly elevated in neonates with confirmed sepsis compared to other groups (p<0.001). Values of (α_1AGP) in suspected group after 48 hours showed elevation and a positive significant relationship with neonatal mortality. Values of α_1AGP were significantly higher in neonates who died due to sepsis in all groups. **Conclusion:** We concluded that α_1AGP and CRP are good predictor markers for detection of early onset sepsis (EOS).

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1. Introduction

Neonatal sepsis is defined as a clinical syndrome of bacteremia with systemic signs and symptoms of infection in the first 4 weeks of life (Anderson Berry *et al.,* 2014)[1].

When pathogenic bacteria gain access into the blood stream, they may cause overwhelming infection (septicemia) or may get predominantly localized to the lung (pneumonia) or the meninges (meningitis) (Paolucci *et al.,* 2012)[2].

The World Health Organization (WHO) estimates that 45% of deaths in under-five years occurring during their first month of life (Kari *et al.,* 2014)[3]. Almost one million deaths occur on day of birth and close to two millions die in the first week of life. Incidence of neonatal sepsis varies from 1-4/1000 live births in developed countries to 10-50/1000live births in developing countries (Made, 2011)[4]. Incidence in Egypt was found to be 37-50% causing death in 50% or more of proved cases (Shehab Eldin *et al.,* 2015)[5].

The susceptibility of a neonate to sepsis is multifactorial. Incidence is influenced by economic status, mode of delivery, sex, maturity and standard of neonatal care received (Shane and Stoll, 2014)[6]. Manifestations of neonatal septicemia are often vague and demand a high index of suspicion for early diagnosis. The most common and characteristic manifestation of late onset sepsis is alteration of well-established feeding behavior, in early onset sepsis respiratory distress is common, apneic spells or gasping may be the only signs (Utomo, 2010)[7].

Early onset sepsis starts before 72 hours of life, causative organisms are prevalent in the maternal genital tract or in the delivery area. Late onset septicemia is caused by organisms from external environment of home or hospital (Jones *et al.,* 2012)[8].

Accurate and timely diagnosis of early onset neonatal sepsis remains challenging to the clinicians and the laboratory (Khair *et al.,* 2012)[9]. Various strategies to reduce morbidity and mortality involve

the use of clinical signs with hematological and serological markers (Srinivasan and Harris, 2012)[10].

Alpha-1 acid glycoprotein is one of lipocalin family and member of acute phase protein, it appears to function in modulating the activity of the immune system during the acute phase reaction (Smith *et al.,* 2012)[11].

High levels of α-1AGP were detected in 85% of infants with severe bacterial infections. 26% of sick infants without infection had a slightly elevated α1AGP level which decreased rapidly. In bacterial infection, the serum α1AGP concentration followed the clinical course. Thus α-1AGP concentration was a useful parameter for diagnosis and monitoring of bacterial infection in neonates (Sann *et al.,* 2009)[12].

Aim of work:

The present study aimed to estimate α-1AGP as an early indicator for the diagnosis of EOS in fullterm neonates and its relationship to outcome of patients.

Objectives:

Assessment of α-1AGPas a marker in diagnosis of EOS in fullterm and its role compared to CRP. Also, α-1AGP is compared upon diagnostic suspicion and 48 hours later.

Correlation between α-1AGP and mortality in neonatal sepsis to be estimated as well.

2. Subjects and Methods:

This is a prospective case control study conducted on full term neonates up to 7 days of life, admitted to the neonatal intensive care unit of Suez Canal University hospital during the period from May 2013 to August 2014. It included 65 neonates classified into 3 groups. First, confirmed cases, 30 neonates presenting with sepsis confirmed clinically and with a positive blood culture. Second, suspected cases, 15 newborns with clinical features of sepsis and non-specific lab markers. Third, controls, 20 newborns who were apparently healthy term newborns delivered in the SCU hospital and come for follow up in our well baby clinic.

Inclusion criteria: All neonates delivered full term and with risk factors of developing EOS such as premature rupture of membrane, difficult or instrumental delivery and maternal urinary tract infection were included. Neonates with clinical presentation suggesting sepsis as temperature instability, shock, hypoperfusion, respiratory distress or apnea, bleeding, convulsions, skin motling and inability to take feed were included. Neonates with laboratory evidence of sepsis in the first 72 hours according to HSS (hematological sepsis score).

Exclusion criteria: All neonates with conditions that can affect α-1AGP level other than sepsis such as neonatal birth trauma, surgical intervention, with masses or congenital anomalies or given corticosteroids.

Methods:

All neonates were subjected to full history taking and full clinical examination and laboratory investigations including blood picture, CRP and blood culture for hematological sepsis score.

Sample collection: 2 ml venous sample was collected under aseptic technique, 1 ml for CBC and CRP on EDTA; 1 ml for α-1AGP allowing sample to clot for 30 minutes and centrifuged for 10 minutes and serum stored at -20. 4-5 ml were collected in special tubes for blood culture taken before antibiotic therapy. α-1AGP is measured by single radial immunodiffusion on agarose gel impregnated with anti-species α-1AGP serum, using kits. α-1AGP present in the serum formed an immunoprecipitate with α-1AGP antiserum. The resulting change in turbidity was measured spectrophotometrically at 340 nm. The levels >52 mg/dl during the first 48 hours were considered positive. We used the hematological scoring system (HSS) for early diagnosis of neonatal sepsis based on total WBCs count, immature: total neutrophils count, immature :mature neutrophils count and platelet count. If score≤2 it means sepsis is very unlikely, if score is 3 or 4 it means sepsis is possible, and if score ≥5 sepsis or infection is very likely.

Data management and statistical analysis:

All data were coded computerized, they were presented in order of frequency and percentage and tabulated in graphs and tables by Excel 2003 for windows. Chi-square test was used for qualitative data to find out the difference between variables and to detect significant associations of data. T-test was used for detection of difference quantitative data. Data was summarized as mean ± standard deviation. Comparisons between more than two different groups were performed using Anova variation and Bonferronitest. Pearson correlation was done for correlation between variables, P-value fixed at 5% level where, $p>0.05$: non-significant, $p<0.05$: significant difference, $p<0.001$: highly significant difference. Receiver operating characteristic (ROC) curve and odds ratio were used to differentiate between the markers.

Ethical considerations:

We received a consent from parents of all neonates participating in our research and were informed about the objectives of the study and details of study steps. Confidentiality of the information was guaranteed, no personal data was published. Agreements from the responsible authorities was obtained, from ethical committee of faculty of medicine Suez Canal University Institute. The subjects did not pay for this research and did not pay for the investigations, they had the right to withdraw at any time from the study. All left over samples if any were discarded at once and not used in any other research.

3. Results

This study was held in Suez Canal University NICU from May 2013to August 2014, our objectives were to measure α-1AGP value as a marker in diagnosis of EOS in fullterm neonates compared to CRP and to estimate the relationship between α-1AGP level and mortality in neonatal sepsis.

Our study included 65 neonates; 30 neonates confirmed to have sepsis with positive blood culture, 15 neonates suspected to have sepsis with positive acute phase reactants and positive score of the HSS and 20 healthy neonates.

Confirmed cases mean gestational age was 38.1±0.9 weeks, suspected cases mean gestational age was 37.6±0.6 weeks and healthy neonates mean gestational age was 38.5±1.2 weeks.

The most frequent symptoms and causative organisms detected in infected group I are illustrated in table 2 and table 3.

Some laboratory investigations as thrombocytopenia, increased sedimentation rate and Immature/Total neutrophil ratio as part from hematological sepsis score (HSS) showed a statistically significant difference between the 3 groups. We showed a significantly high CRP level for confirmed and suspected sepsis which was positively related to neonatal deaths. α-1AGP levels were significantly elevated in neonates with confirmed sepsis compared to other groups.

Table [1]: Comparison of demographic and fetal risk factors among the studied three groups

		Control group (n=20)		Confirmed cases (n=30)		Suspected cases (n=15)		*p*-value
Multiple pregnancy	Single	19	95%	28	93.33%	14	93.33%	0.9 (NS)
	Twin	1	5%	2	6.67%	1	6.67%	
Neonatal sex	Male	10	50%	18	60%	8	53.33%	0.8 (NS)
	Female	10	50%	12	40%	7	46.67%	
Mode of delivery	ND	16	80%	20	66.67%	8	53.33%	0.2 (NS)
	CS	4	20%	10	33.33%	7	46.67%	
Birth weight (gm)	Mean ± SD	3060 ± 300[a]		2570 ± 500[b]		2850 ± 500[ab]		0.001*
Gestational age (weeks)	Mean ± SD	38.5 ± 1.2 [a]		38.1 ± 0.9 [ab]		37.6 ± 0.6 [b]		0.04*
Apgar score 1 min**	Mean ± SD	5.8 ± 1.4		5.9 ± 1.15		6.4 ± 1.1		0.3 (NS)
Apgar score 5 min**	Mean ± SD	8.15 ± 0.8		8.1 ± 0.8		8.5 ± 0.6		0.3 (NS)

*Statistically significant difference NS: no statistically significant difference

[a], [b] indicate statistically significant difference within groups (Bonferroni test).

**APGAR score is used as an indicator of the infant's condition in the first and fifth minutes after birth that include appearance, heart rate, muscle tone, respiratory effort and activity.

Table [2]: Distribution of clinical manifestations among confirmed and suspected cases

Manifestation	Confirmed(n=30) No	%	Suspected(n=15) No	%
Fever	20	66.67%	8	53.3%
Poor feeding	16	53.33%	8	53.3%
Tachypnea	16	53.33%	6	40%
Jaundice	12	40%	5	33.3%
Skin Motling	12	40%	4	26.67%
Tachycardia	10	33.33%	3	20%
Abdominal distention	9	30%	3	20%
Lethargy	8	26.67%	2	13.3%
Vomiting	7	23.33%	2	13.3%

Table [3]: Distribution of blood culture results among the studied patients in confirmed group

Organism	Number	Percentage
E. coli	8	26.67%
Klebsiella	7	23.33%
Staph. Aureus	6	20%
Pseudomonas	4	13.33%
Staph. Epidermidis	2	6.67%
Streptococci	2	6.67%
Enterobacter	1	3.33%

Table [4]: Comparison of α1-AGP and CRPamong the studied neonates in three groups

		Control group (n=20)	Confirmed cases (n=30)	Suspected cases (n=15)	*p*-value
α1-AGP (mg/dl)	Mean ± SD	25.5 ± 16.49 [a]	122.8 ± 66.1 [b]	49.9 ± 25.76 [a]	0.001*
CRP (mg/l)	Mean ± SD	5.32± 2.9	40.88 ± 37.97	22.73 ± 20.27	0.001*

*Statistically significant difference

[a], [b] indicate statistically significant difference within groups (Bonferroni test)

Table [5]: Comparison between The mean values of α1-AGP on suspicion and after 48 hours in the suspected group

		Suspected cases (n=15)		*p*-value
		On suspicion	After 48 hours	
α1-AGP (mg/dl)	Mean ± SD	49.9 ± 25.76	88.13 ± 29.13	0.001*

*Statistically significant difference

Table [6]: Relation between α1-AGP valuein three groups and morality

		Control group (n=20)	Confirmed cases (n=30)	Suspected cases (n=15)	*p*-value
		Mean ± SD (α1-AGP value)	Mean ± SD (α1-AGP value)	Mean ± SD (α1-AGP value)	
Mortality	Alive	25.5 ± 16.49 [a]	107.5 ± 54.77 [b]	45.8 ± 24.49 [a]	0.001*
	Deceased	-	199.4 ± 69.7	76 ± 22.6	0.07 (NS)
p-value		-	0.003*	0.1 (NS)	

NS: no statistically significant difference

[a], [b] indicate statistically significant difference within groups (Bonferroni test).

Table [7]: Relation between α1-AGP value (after 48 hours)in suspected group and morality

Suspected Cases (n=15)	**Alive**	**Dead**	***p*-value**
Mean value ofα1-AGP ±SD	80.23 ±16.5	139.5 ±50.2	0.003*

*statistically significant difference

Table [8]: Relation between first value of α1-AGPand diagnosis of EOS

		α1-AGP				*p*-value	Odds ratio (95% CI)
		> 52		≤ 52			
Sepsis	Confirmed/suspected	34	94.4%	11	37.9%	0.001*	27.8 (5.1 – 266.9)
	No sepsis	2	5.6%	18	62.1%		
Sensitivity		94.4%					
Specificity		62.1%					
PPV		75.6%					
NPV		90%					
Accuracy		80%					

*Statistically significant

Table [9]: Relation between CRP and diagnosis of EOS

		CRP				*p*-value	Odds ratio (95% CI)
		+ve		-ve			
Sepsis	Confirmed/suspected	36	90%	9	36%	0.001*	16 (3.74 – 78.1)
	No sepsis	4	10%	16	64%		
Sensitivity		90%					
Specificity		64%					
PPV		80%					
NPV		80%					
Accuracy		80%					

*Statistically significant

Table [10]: Relation of α1-AGP and CRP values and neonatal mortality among infected group

	Alive	**Dead**	***p*-value**
α1-AGP >52mg/dl(n=36)	29 (80.5%)	7 (19.4%)	0.3(NS)
CRP>6mg/l	33 (82.5%)	7 (17.5%)	0.3(NS)

4. Discussion:

The most frequent symptoms detected in confirmed and suspected sepsis groups in our study were temperature instability, poor feeding, and tachypnea and the least were lethargy, tachycardia and abdominal distension matching with El-kerdani, 2001, Mahmoud 2006 and Hafsal *et al.,* 2011.[13,14,15]

Regarding causative organisms of neonatal sepsis, Shim and his colleagues in 2011[16] mentioned that they vary from one geographic area to another and from one nursery to the other. Despite that, we had similar results as Mohamed in 2005, Ali *et al.,* 2004 and Muley *et al.,* in 2015.[17,18,19.] The most frequent organisms were E *coli* (26.7%), Kleibsella (23.3%), *Staph aureus* (20%) and pseudomonas (13.3%). The least were *Staph epidermidis*, streptococcus species and enterobacter.

Many markers of neonatal sepsis have been suggested such as CRP, PCT, IL-6, α-1AGP and TNF-α. However, best single biochemical marker or combination of markers for early detection of neonatal sepsis has not been derived (Haining *et al.,* 2013 and Labib *et al.,* 2013).[20,26]

CRP is still used as routine investigation for diagnosis and management in most of neonatal sepsis practice guidelines (EMA, 2010)[27].

In the current study, CRP was positive in 25 cases of confirmed group and negative in only 5 cases. In suspected group, CRP was positive in 11 cases and negative in 4 cases. Furthermore, confirmed and suspected had significantly higher levels of CRP compared to control group.

For those 25 CRP positive cases of confirmed group only 5 died (20%); and from those 11 suspected cases group only 2 died (18%). Thus, there was a non-significant relationship between CRP and death in confirmed and suspected groups mismatching with Mostafa *et al.,* in 2011.[21]

In some studies with cutoff value 10mg/l for CRP, the reported statistical outcomes were as follows: sensitivity 70% to 93%, specificity 41% to 98%, positive predictive accuracy 6% to 83% and negative predictive accuracy 97% to 99% (Dollner *et al.,* 2001).[28]

Some researchers in Iran compared CRP to some inflammatory mediators as parameters for early diagnosis of neonatal sepsis; CRP 12mg/l was found to be the most appropriate cutoff value by using receiver operating characteristic (ROC) curves, and at this cutoff value, test sensitivity was 45%, specificity was 95%, PPV was 30% and NPV was 30%.[29]

By using ROC curve in our study, CRP 12.2mg/l was found to be the most appropriate cutoff value. Area under curve was 0.8, sensitivity (90%), specificity (64%), PPV(80%), and NPV (80%).

α-1AGP is one of the acute phase proteins in humans, its serum concentration increase in response to tissue injury, inflammation and infection. It is a useful marker for early detection of certain disease as well as progression (Tesseromatis, 2011).[22]

α-1AGP has not been fully investigated yet for its diagnostic role in neonatal sepsis, some authors found that it is a promising marker (Ipek *et al.,* 2010).[23]

α-1AGPhad significantly high mean values (122.8±66.1 mg/dl) in our confirmed group compared to (49.9±25.7 mg/dl) for suspected group and (25.5±16.5 mg/dl) for controls.

We collected 2 samples from suspected group. First α-1AGP serum level upon sepsis suspicion was 49.9±25.7 mg/dl which increased considerably in second sampling after 48 hours to 88.13±29.13 mg/dl, El-Gohary *et al.,* in 2014 reported similar results and recommended serial measurements for suspected early onset sepsis.[24]

In our study based on previously reported cutoff values of α-1AGP (>52mg/dl) and sepsis diagnosis for infected cases(confirmed and suspected) showed statistical outcomes as follows: sensitivity was 94.4%, specificity was 62.1%, PPV was 75.6%, NPV was 90%, accuracy was 80%,odds ratio was 27.8 and *p*-value was 0.001. Also, at a lower level of α-1AGP>39mg/dl (confirmed and suspected groups) area under ROC curve was 0.88, sensitivity 80%, specificity 90%, *p*-value=0.001, meant it had a high sensitivity and specificity as a marker of EOS prediction.

For suspected group only, at the α-1AGP level =>39mg/dl (1st reading cut off value), reported statistical outcomes were; area under ROC curve 0.78, sensitivity 60%, specificity 90%, PPV 82%, NPV 75% and p value was 0.001; its high specificity accompanied with low sensitivity means that a single α-1AGP test in early suspected neonatal sepsis is of limited value, so serial measurements are suggested.

Ipek and his colleges in 2010 evaluated the diagnostic value of CRP and α-1AGP in EOS diagnosis, he found that CRP had limited value in early diagnosis, and as a single test of α-1AGP had limited usefulness in early diagnosis and suggested serial α-1AGPtesting.Wander *et al.,* in 2012 had similar results.

Regarding levels of α-1AGP and CRP as markers for prediction of mortality among infected cases (group I and II).Out of 40 cases with CRP more than 12 mg/l, only 7 died and out of 36 cases with α-1AGP more than 52 mg/dl, only 7 died. The relationship between both CRP and α-1AGP levels and mortality among the infected group as a whole (group I andII) was statistically non- significant despite that α-1AGP serum values were considerably higher in deceased

neonates (139.5± 50.2 mg/dl) than living neonates (80.23±16.5 mg/dl).[23,25]

References

1. Anderson Berry, Belling LL, Ohning BL. Neonatal sepsis. In eds. Macgilvray SS, Windle ML, Clark DA and Wagner CL. e-medicine review article in neonatology, 2014.
2. Paolucci M, Landini MP and Sambri V. How can the microbiologist help in diagnosing neonatal sepsis? International journal of Pediatrics; article ID 120139, 14 pages, 2012.
3. Kari A Simonsen, Ann L Anderson, Shirley. FDelair and H. Dele Davies. Early onset sepsis. Clin Microbiol Rev;27(1):21-47,2014.
4. Made IK. Incidence and factors associated with mortality of neonatal sepsis. Pediatrindones J; vol.51, No 3, 2011.
5. Shehab Eldin Eman, Mohamed Elsokary, Mohamed Reda Basiouny and Ramadan Hassan. Epidemiology of neonatal sepsis and implicated pathogens. A study from Egypt. Biomed Research International; vol 11, 2015.
6. Shane Al and Stoll BJ. Neonatal sepsis: progress towards improved outcomes. J infect; 68 suppl 1: S24-32, 2014.
7. Utomo MT. Risk factors of neonatal sepsis: a preliminary study. Indonesian journal of tropical and infectious disease; vol 1:23-26, 2010.
8. Jones AR, Kuschel C, Jacobs S and Doyle LW. Reduction in late onset sepsis on relocating a neonatal intensive care nursery. Journal of pediatrics and child health; vol.48, Issue 10, 891-895, 2012.
9. Khair KB, Rahman MA, Sultan T, Roy CK, Rahman MQ and Ahmed AN. Early diagnosis of neonatal septicemia by hematological scoring system, C-reactive protein and serum haptoglobin. Mymensingh MED J; 21(1):85-92, 2012.
10. Srinivasan L and Harris MC. New technologies for the rapid diagnosis of neonatal sepsis. Curr Opin Pediatr; 24(2):165-171, Apr 2012.
11. Smith KD, Behan J, Mattews-Smith G and Magliocco AM. Alpha-1-acid glycoprotein as a potential biomarker for breast cancer. Genetics and molecular biology; Ch 9:201-222, 2012.
12. Sann L, Bienvenu J, Lahet C, Divry P and Cotte J. Serum orosomucoid concentration in newborn infants. Clin Chem;27(5):721-726, 2009.
13. El-Kerdani TA. Value of neutrophil CD 11b expression of interleukin-6 and soluble receptors. Egypt J. neonatal; 2(2):116-119, 2001.
14. Mahmoud MR. Bacteriological profile of neonatal septicemia in Zagazig University NICU. Thesis submitted in partial fulfillment for M.Sc. degree in Pediatrics. Faculty of medicine Zagazig University 2006.Available on www.eulc.edu.eg.
15. Hafsal A, Fakrruddin M, Hakim MA and Sharma JD. Neonatal bacteremia in a neonatal intensive care unit: Analysis of causative organisms and antimicrobial susceptibility. Bangladesh J of Medical Science; vol 10 No 3, 2011.
16. Shim GH, Kim SD, Kim HS, Kim ES, Lee HJ, Lee JA, *et al*. Trends in epidemiology of neonatal sepsis in a tertiary center in Korea. J Korean Med Sci; 26(2):284-9, 2011.
17. Mohamed IH.Study of birth canal colonization in relation to early onset sepsis in full term infants. Thesis submitted for fulfillment for Master degree in obstetrics and gynecology. Faculty of Medicine Zagazig University, 2005.Available on www.eulc.edu.eg.
18. Ali SA, Khan TA and Zaidi AK. Neonatal sepsis in Peshawar. Arch. Dis. Child; 89:568-571, 2004.
19. Muley VA, Ghadage DP and Bhore AV. Bacteriological profile of neonatal septicemia in tertiary care hospital from Western India. J Glob Infect Dis; 7(2):75-7, 2015.
20. Haining Y, Jie H, BokunLv, *et al*. Diagnosis value of the serum amyloid A test in neonatal sepsis. Bio Med research international; vol 2013:page9, 2013.
21. Mostafa MS, Mounir ZM, Waheed H, El-Gamal HA, Morcos WH, Emara NA and Eltaae Wh. Serum amyloid A an early diagnostic marker for neonatal sepsis. Life science journal; 8(3):271-277, 2011.
22. Tesseromatis C, Alevizou A, Tigka E and Kotsiou A. Acute phase proteins: alpha 1 acid glycoprotein, regulation and functions of acute phase proteins; ISBN:953-978, in tech, DOI:10.5772/22640, 2011.
23. Ipek IO, Saracoglu M and Bozaykut A. Alpha 1-acid glycoprotein for the early diagnosis of neonatal sepsis. J Matern Fetal Neonatal Med; 23(7):617-21, 2014.
24. El-Gohary T El-Sayed, El-Nady M Nasih and Mahmood AA. Role of alpha-1-acid glycoprotein in comparison to CRP in diagnosis of neonatal sepsis. Thesis for fulfillment of master degree in Pediatrics, Banha University, 2014.Available on www.eulc.edu.eg.
25. Wander K, Brindle E and O'Connor KA. Sensitivity and specificity of C-reactive protein and alpha-1-acid glycoprotein for episodes of acute infection among children in Kilimanjaro, Tanzania. Am J Hum Biol; 24(4):565-8, 2012.
26. Labib AZ, Mahmoud AB, Eissa NA, El Gendy FM, Soliman MA and Aly A. Early diagnosis of neonatal sepsis: a molecular approach and detection of diagnostic markers versus conventional blood culture. Intl. J. Microbiol. Res;4(1):77-85, 2013.
27. NICE guidance CG 149.antibiotics for early onset neonatal infection. Report on the expert meeting on neonatal and pediatric sepsis .August 2012. European medicines agency EMA/477725/2010 London.
28. Dollner H, Vatten L and Austgulen R. Early diagnostic markers for neonatal sepsis: comparing c-reactive protein, interleukin-6, soluble tumor necrosis factor receptors and soluble adhesion molecules. J. Clinic Epidemiol ;54:251-257, 2001.
29. Minoo Adib, Zahara Bashshiani, Fakhri Navaei, Fereshteh Saheb Fosoul, Salomeh Fouladi and Hamidreza Kazemzadeh. Procalcitonin: A reliable marker for the diagnosis of neonatal sepsis. Iran J Basic Med Sci; vol 15,no 2:777-783, 2012.