Introduction

Neonatal sepsis is a bacterial infection in the blood. It is found in infants during the first month of life. Despite major advances in neonatal intensive care, neonatal sepsis continues to be an important cause of morbidity and mortality. Therefore, it is important to diagnose neonatal sepsis early and accurately ***(Cekmez et al., 2011).***

Despite extensive investigation, no single test meets the criteria that would make it an ideal marker for early diagnosis of sepsis in the newborn. Generally, screening includes a complete blood count with differential and may be accompanied by other adjuvant tests such as a C-reactive protein (CRP) ***(Hawak, 2008)***.

A new hormone has been identified that links obesity to type 2 diabetes. It has been called resistin (for "resistance to insulin"). Resistin is expressed in white adipose tissue and is induced during adipogenesis. It is one amongst a family of three proteins, known as resistin-like molecules (RELMs), which have a conserved pattern of 11 cysteine residues at the C-terminal end of the structure ***(Steppan et al., 2001).***

Serum level of resistin is increased dramatically by endotoxemia in humans, and correlate with a marker of inflammation in patients with type 2 diabetes. Thus, systemic inflammation leads to increased resistin production and

circulating levels in humans. The increased level of resistin in humans with obesity is likely an indirect result of elevated levels of inflammatory cytokines characteristic of states of increased adiposity. Hence, obesity and acute inflammation are both hyper-resistinemic states associated with insulin resistance ***(Lehrke et al., 2004).***

Resistin has recently been recognized to act as a proinflammatory cytokine in humans. Patients with severe sepsis or septic shock had significantly elevated systemic levels of resistin, which correlated with severity of disease ***(Johansson et al., 2007).***

Aim of the Work

The aim of this study is to evaluate the predictive value of resistin in neonatal sepsis, and to compare these adipocytokine with C-reactive protein (CRP).

I- NEONATAL SEPSIS

Definition:

Neonatal sepsis, sepsis neonatorum, and neonatal septicemia are terms that are used to describe the systemic response to infection in the newborn infant. The criteria for neonatal sepsis should include documentation of infection if a newborn infant had a serious systemic illness (in which non-infectious explanations for the abnormal pathophysiologic state are excluded or unlikely). Neonatal sepsis is a disease of infants who are younger than one month of age, critically ill, and have a positive blood culture ***(Stoll, 2008)***.

Many focal infections such as meningitis, pneumonia and urinary tract infection that can occur in other age groups may occur in neonates as well, but infections in neonates have unique elements that differ from those in older age groups. In neonates, focal signs and symptoms due to localized infections may be clinically imperceptible and thus difficult to differentiate on initial presentation from generalized blood stream infections ***(Baltimore, 2002).***

Bacterial sepsis and meningitis continue to be the major causes of morbidity and mortality in the newborn. This is despite improvements in antimicrobial therapy, advances in neonatal life support measures, and the prompt recognition of the prenatal risk factors for infection. Sepsis neonatorum can be devastating and surviving infants that have significant neurologic sequel as a consequence of central nervous system

involvement, septic shock, or hypoxemia secondary to severe parenchymal lung disease or persistent pulmonary hypertension ***(Feigin et al., 2002).***

Table (1): Definitions of Systemic inflammatory response syndrome and sepsis: pediatric patients SIRS:

The systemic inflammatory response to a variety of clinical insults, manifested by 2 or more of the following conditions:
Temperature instability <35^{o}C or > 38^{o}C.
Respiratory dysfunction
Tachypnea>2SD above the mean for age
Hypoxemia (PaO2<70mmHg on room air)
Cardiac dysfunction
Tachycardia<2SD above the mean for age
Delayed capillary refill < 3sec
Hypotension < SD below the mean for age
Perfusion abnormalities
Oliguria (urine output <0.5ml/Kg/hr)
Lactic acidosis (elevated plasma lactate and / or arterial pH < 7.25)
Altered mental status
Sepsis: the systemic inflammatory response to an infectious process.

(Adams Chapman and Stoll, 2001)

Incidence:

The rate of sepsis in infants born at any hospital varies according to the prenatal risk factors in the community of women who deliver there. Economic standards, availability of prenatal care, geographic variations, and outbreaks of cases caused by particular species of pathogen may each play a role in determining the overall rate ***(Lott, 2003).***

Over all incidence of neonatal sepsis ranged from 2 to 20 per 1000 live births with cases fatality rates of 1 to 69%, the incidence of culture proven sepsis in the united states is approximately 2 in 1000 live births of the 7-13% of the neonates who were evaluated for neonatal sepsis, only 3-8% had culture proven sepsis. The early signs of sepsis in the newborn are non specific, therefore, many newborns undergo diagnostic studies and the initiation of treatment before the diagnosis has been determined ***(AAP, 2003).***

American Academy of Obstetrics and Gynecology (AAOG) and Centers for Disease Control and Prevention (CDC) all have recommended sepsis screening and/or treatment for various risk factors, for evaluation of symptomatic neonates. Because the mortality rate of untreated sepsis can be as high as 50%, most clinicians believe that the hazard of untreated sepsis is too great to wait for confirmation by positive cultures; therefore most clinicians initiate treatment while waiting culture results ***(CDC, 2005).***

The incidence of bacterial sepsis and meningitis, especially for gram negative enterobacilli is higher in males than in females, for reasons that are not clear. Male: female ratio is 2:1. Studies have shown that premature infants have an increased incidence of sepsis. The incidence of sepsis is significantly higher in infants with very low birth weight (<1000g), at 26 per 1000 live birth, than in infants with a birth weight of 1000-2000g, at 8-9 per 1000 live births ***(Bellig, 2004).***

Classification:

Neonatal infections are usually classified according to time and mode of transmission. They are grouped into three categories:

1- Congenital infection, acquired in-utero by vertical transmission with onset before birth.

2- Early-onset neonatal infections, acquired by vertical transmission in the prenatal period, either shortly before or during the process of birth.

3- Late and late-onset neonatal infections acquired by horizontal transmission in the nursery. This is shown in table (3) ***(Baltimore, 2002).***

Table (2): Current predominant pathogens in early and late onset sepsis

Early-onset:
Group B *streptococcus*
E. coli.
Listeria Monocytogenes
Staphylococcus aureus
Other *streptococci*
Other gram negative organisms:
Homophiles influenza
Klebsiella pneumoniae
Pseudomonas aeruginosa
Enterobacter species
Late-onset:
Coagulase-negative *staphylococci*
Klebsiella pneumoniae
Pseudomonas aeruginosa
Other gram negative enteric bacteria
Candida species

(Hoffman and Harris, 2002)

Table (3): Relationship of time of onset of neonatal infection and mode of transmission of infection

Time of onset	Age of infection onset	Mode of infection transmission	Major risk factors	Most common organisms
Prenatal	Prior of birth	Transplacental or ascending	Maternal infections, usually primary infection prolonged rupture of membranes	Cytomegalovirus Syphilis Toxoplasmosis Maternal vaginal flora Human immunodeficiency virus.
Early onset	Birth to 2-6 days	Maternal flora transmitted peripartum	Prolonged premature rupture of membranes. Prematurity, septic or traumatic delivery, fetal anoxia, Male sex, Maternal infection (especially urogenital), maternal poverty, preeclampsia, cardiac disease, diabetes mellitus	Eacherichia coli, Group B streptococcus Klebsiella pneumonia Enterococcus Listeria monocytogenes Other enteric gram negative bacilli Species.
Late onset	≥7to30days	Nosocomial	Intravascular catheters, Endotracheal intubation, Assisted ventilation, surgery including necrotizing enterocolitis, Contact with hands of colonized personnel, Contact with contaminates equipment	Those causing early onset sepsis Staphylococcus aureus Coagulase-negative staphylococci Pseudomonas aeruginosa Candida
Late-late onset	> 30days	Nosocomial	Indwelling intravascular devices, Extreme prematurity, Bronchopulmonary dysplasia Ahort gut syndrome, Complex congenital malformations, Previous broad spectrum antibiotic therapy	Staphylococcus aureus Coagulase negative staphylococci Pseudomonas aeruginosa Candida Antibiotic resistant gram-negative bacilli species

(Baltimore, 2002)

Pathogenesis:

The uniqueness of neonatal infections is due to a number of factors

(1) There are diverse modes of transmission of infectious agents from mother to fetus or newborn infant as transhematogenous spread, Vertical transmission of infection in-utero, and exposure to infectious diseases in the nursery or in the community.

(2) The newborn infant may be less capable of responding to infection owing to one or more immunologic deficiencies.

(3) Co-existing diseases of the newborn often complicate the diagnosis and management of neonatal infections for example; acidosis impairs the function of polymorph nuclear leukocytes.

(4) The manifestations of infectious diseases in the newborn infant are extremely variable.

(Bang et al., 2005)

Transplacental transmission of infection to the fetus is variable. The placenta often functions as an effective barrier to prenatal infections that are known to be transmitted transplacentally including Syphilis, Rubella, Cytomegalovirus (CMV), parvovirus B19, Human immunodeficiency virus (HIV), Varicella zoster, Herpes simplex virus I and II, Listeria monocytogenes, Toxoplasmosis, and Tuberculosis ***(Bopanna et al., 2001).***

The fetal environment within the amniotic membranes is normally sterile until onset of labor and delivery occurs. Procedures disturbing the integrity of the uterine contents, such as amniocentesis, cervical cerculage, transcervical chorionic villous sampling or percutaneous umbilical blood sampling can permit entry of skin or vaginal organisms causing amnionitis and secondary fetal infection ***(Baltimore, 2002).***

Prenatal infections are acquired just before or during delivery with vertical transmission of the microorganism from the mother to the newborn infant, the organisms may be bacteria that colonize in the birth canal such as Group B Streptococci, Gonococci, L. monocytogenes, Escherichia coli (particularly the K_1 capsular strain), Chlamydia, Genital Mycoplasma, and Ureaplasma or viruses such as Herpes simplex virus, Coxsackie virus, or fungi as Candida species ***(Oddie and Embleton, 2002).***

Many infants suffering from sepsis are symptomatic at birth, however, others remain relatively asymptomatic until the infection is well established, often resulting in delayed therapy and a high morbidity rate. Microorganisms acquired by the infant during birth colonize on the skin and mucosa of nasopharynx, oropharynx, conjunctiva, umbilical cord and external genitalia of the female infant ***(Bang et al., 2005).***

The skin of infants delivered by caesarian section is sterile soon after birth in contrast to that of infants born through the vagina, who are colonized with organisms from the birth canal during the neonatal period in which the skin is

functionally and anatomically immature so permeability is increased and susceptibility to blister formation in the neonate increased ***(Schuchat et al., 2000)***.

Transient bacteremia may accompany procedures that traumatize mucosal membranes as endotracheal suctioning, the bacteremia may also occur by direct extension from colonized mucosal surfaces ***(Goldstein et al., 2005).***

Invasion of the blood stream may follow multiplication of organisms in the upper respiratory tract. The source of bacteremia is frequently in apparent, but careful inspection may reveal a focus, such as an infected circumcision site or infection of the umbilical stump. Metastatic foci of infection may follow bacteremia and may involve the lungs, kidney, spleen, bones or central venous system ***(Auriti et al., 2003).***

The majority of infants cared in a neonatal intensive care unit are exposed to a variety of diagnostic and therapeutic procedures that may compromise host defenses and provide portal of entry for organisms. The extensive use of antibiotics in the neonatal intensive care units may alter the low birth weight infant's normal bacterial flora and lead to cross-infection with antibiotic – resistant organisms carried on the hands of personnel or on contaminated equipment and so postnatal neonatal infections are acquired after birth during the first 28 days of life, it may be transmitted from a variety of human sources such as family contacts, hospital personnel or from sources such as contaminated equipment ***(Bang et al., 2005).***

Etiology:

Maternal, neonatal and environmental risk factors determine which infants exposed to potentially pathogenic organisms will develop sepsis, meningitis or other serious invasive infections ***(Avery, 2006).***

(A) Maternal Risk Factors:

The attack rates of neonatal sepsis increase significantly in the presence of maternal risk factors, namely premature rupture of membranes (PROM), maternal intrapartum fever, maternal leukocytosis, chorioamnionitis and vaginal colonization with Group B Streptococci ***(Lott, 2003).***

Prenatal infections are acquired just before or during delivery with vertical transmission of the microorganism from mother to newborn infant. The human birth canal is a host to large number of aerobic and anaerobic bacteria, Mycoplasma, Chlamydia, fungi, yeast and viruses. Staphylococcus epidermidis, lactobacilli, diphtheroids, and alpha-hemolytic streptococci are found in 50 to 100% of the vaginal cultures of pregnant women. Significant but less frequent include, Gardinerella vaginalis in 20%, Proteus and Klebsiella in 10% and Group D Streptococci in 10-40%, others but less common are Citrobacter, Actinobacter and Campylobacter ***(Goldenberg et al., 2000).***

The amniotic infection syndrome usually occurs as a result of prolonged rupture of the chorioamniotic membrane. It may lead to congenital pneumonia or systemic bacterial infection with manifestations becoming apparent prior to delivery (fetal

distress, tachycardia), or after a latent period of a few hours (respiratory distress, shock) ***(Lahra and Jeffery, 2004).***

Transplacental acquisition of bacteria during the course of maternal bacteremia is difficult to establish, but it has been documented in patients infected with Listeria monocytogenes and Treponema palladium ***(Oddie and Embleton, 2002).***

Corticosteroids administered to mothers in anticipation of delivery to enhance pulmonary maturation in the fetus resulted in significant decrease in incidence and severity of neonatal respiratory distress syndrome but an increase in maternal infection and a trend towards increased neonatal infection ***(Yoon et al., 2001).***

Socioeconomic factors appear to be important in determining which infants are at risk of infection. Premature infants and infants with low birth weight are more frequently born to mothers of low socioeconomic class than to those of average or high socioeconomic class. The bacterial cause of neonatal sepsis and meningitis varies from one geographic area to another ***(Al-Harthi et al., 2000).***

(B) Environmental Factors:

Resuscitation at birth, particularly if it involves endotracheal intubation, insertion of an umbilical vessel catheter, or both, are associated with an increased risk of bacterial infection, possibly due to prematurity or the presence of infection at the time of birth ***(Bizzarro et al., 2005).***

Invasive monitoring and respiratory or metabolic support, also various drains and shunts for hydrocephalus increase the risk of Staph. Epidermidis sepsis ***(Drews et al., 2003).***

Frequent use of broad spectrum antibiotics in the NICU interferes with colonization by normal flora and facilitates colonization of the infant's skin, umbilicus, nasopharynx and gastrointestinal tract by pathogenic bacteria or fungi ***(Sinha et al., 2003).***

Bottle feeding may increase the risk of neonatal infection in comparison to breast feeding as the human milk has a marked protective effect against infection. Even partial breast feeding protects against neonatal sepsis in at risk population ***(Drews et al., 2003).***

Nosocomial infection; neonatal infections acquired in the hospital are nosocomial. Nosocomial infections result in considerable morbidity and mortality among neonates, especially those in neonatal intensive care units. Because most of the early onset infections are acquired intrapartum, infection that develops later than 48-72 hours after birth are usually considered nosocomial ***(Auriti et al., 2003).***

(C) Neonatal Risk Factors:

Low-Birth Weight is the most significant factor associated with sepsis. The overall rate of sepsis reported is eight times higher in 1000 to 1500 grams than in 2000 to 2500 grams infants ***(Schuchat et al., 2000).***

The physiologic immunodeficiency of preterm newborn is the major cause of their increased susceptibility to infections. Although non-specific and specific host defense mechanisms are morphologically intact, there is a multiple functional and quantitative defects ***(Lin et al., 2003).***

Premature delivered infants have lower IgG levels than those delivered at term. The possible explanation could be immature liver functions in preterm and inadequate transfer of IgG across the placenta. Although T cells reach normal levels by 30 to 32 weeks of gestation, and are capable of proliferating as in adult, there is defective cell mediated immunity in the premature and the full term neonates ***(Weber et al., 2003).***

The morbidity and mortality associated with neonatal sepsis is dependent upon the gestational age. Although the survival of premature born with a birth weight less than 1000 grams has improved significantly, this population has multiple risk factors for the development of infections during their stay in the neonatal intensive care unit among them and the frequent use of invasive procedures ***(Goldenberg et al., 2000).***

Male infants have a four fold increased risk to develop sepsis than females. A gene located on the X-chromosome and involved with the function of the thymus or with the synthesis of immunoglobulins has been postulated ***(Auriti et al., 2003).***

Anatomic factors as posterior urethral valve increases liability for urinary tract infection and midline defects in the palate increase the risk of otitis media. Infants with underlying defects may not have systemic infections until passively acquired maternal antibody has dissipated. Because the half life