USE OF ALPHA 1. ACID GLYCOPROTEIN AS A DIAGNOSTIC INDEX IN NEONATAL BACTERIAL INFECTIONS

THESIS

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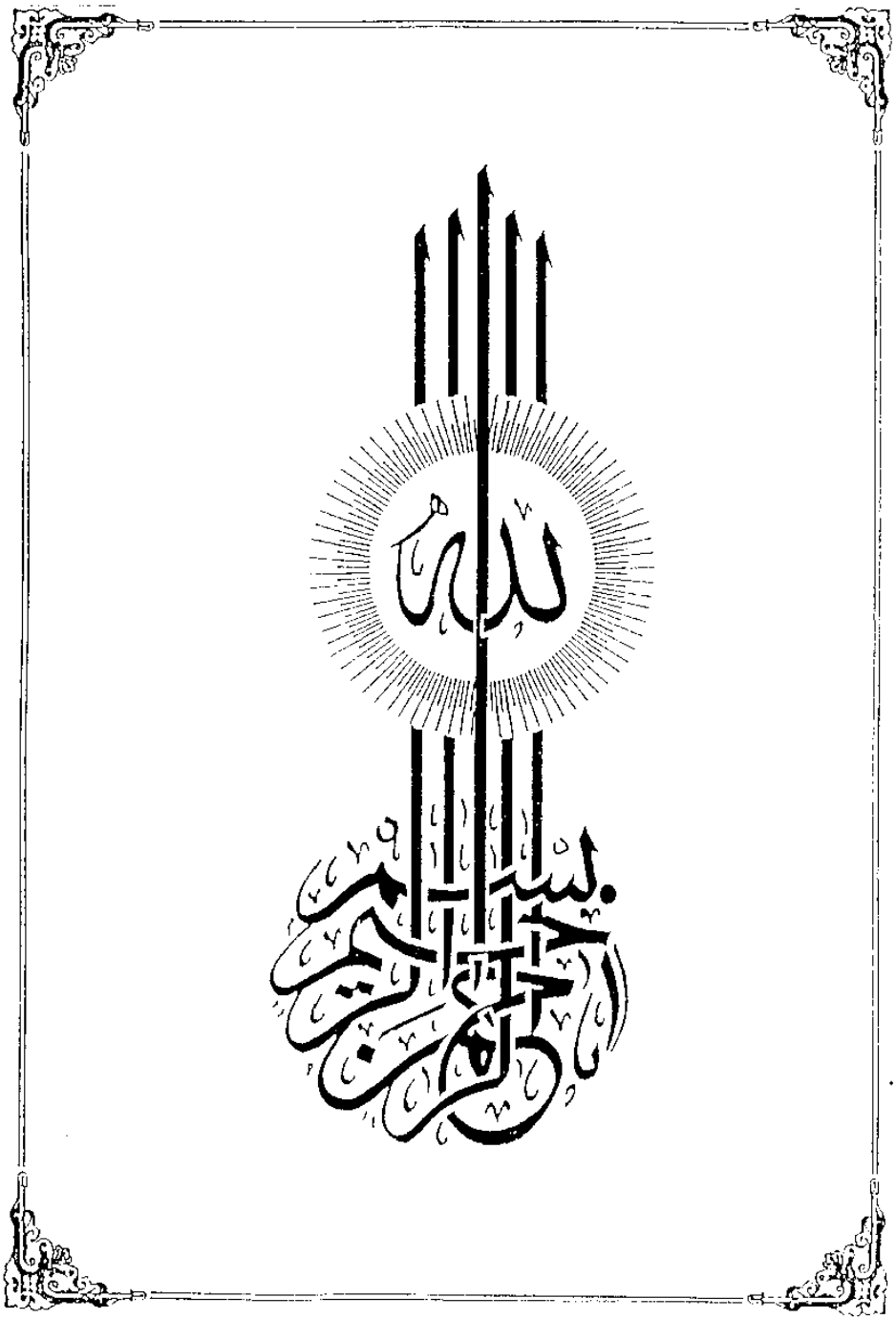

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INTRODUCTION:

Throughout pregnancy and until the membranes rupture, the infant is usually well protected from microbes. Under normal circumstances in the immediate neonatal period the infant is exposed to many micro organisms including aerobic and anaerobic bacteria, viruses, fungi and protozoa (Parkman., 1984).

Acute phase proteins are protein components of plasma, their concenterations increase in response to tissue injury, acute and chronic inflammations and neoplasia (Colley et al., 1983).

Alpha 1 acid glycoprotein is a glycoprotein which is elevated in acute inflammation indicating that it is typically an acute phase reactant protein in human serum (Shibata et al., 1977). It is employed for screening neonatal bacterial infection (Ganrot et al., 1972).

AIM OF THE WORK:

The aim of the work is to demanstrate the changes in the serum level of Alpha. 1-acid glycoprotein "Orosmucaid" in neonatal bacterial infection, to be a usaful diagnostic index.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Acute phase reactants (A.P.R.)

Definition:

The term "acute phase reactants" is generally referred to protein components of plasma, whose concentrations change, mainly increase in response to tissue damage, this increase is attributed to their enhanced synthesis and catabolism (Gewurz et al., 1982). This tissue damage may be induced by a wide variety of stimuli, including tissue injury, acute and chronic in flammation, connective tissue disease and neoplasia (Cooper and Ward, 1979).

Acute phase reactants showed at least two common features. The first feature is that they all contain significant amount of carbohydrates, which protect the folded poly-peptide chain against the action of proteases, after the physical properties of the polypeptide chain such as net charge and solubility, and lastly serve as a blocking agent to cover the specific binding site of the macromolecular constituents of a cell.

The second feature is that they are synthesized in liver parenchymal cells and more precisely by hepatocytes. Hence, acute phase reactants may be defined as truma - inducible, liver-produced plasma glycoproteins (Koj,1974).

COMPONENTS:

Acute phase reactants include several components, those in highest concentration are: Haptaglobin (Ismail et al., 1986).

Alpha 1-antitrypsin, Alpha 1-acid glycoprotein, C_3, ceroloplasima fibrinogen (Ritchie, 1979), and C-reactive protein (El-Essawy et al., 1983). Those in lower concentrations are: Alpha 1- anti-chymotrypsin (Kosaka and Tozauwa, 1976), Hemopexin (Baumann et al., 1984), serum amyloid -A (Kushner et al., 1981), and C9 (Kawashi - Takahashi et al., 1975).

Albumin, transferrin, and prealbumin are considered as negative acute phase reactants i.e they are diminished in the acute phase (Johnson, 1982).

Biochemical properties:

The principal biochemical properties of these proteins are shown in table I (Bienvenu et al., 1984).

Protein	Molecular weight	Peptide content%	Carbohydrate content%	Isoelectric Point
Alpha-1 acid glycoprotein	40,000	63	42	1.82
Alpha-1 antichymotrypsin	68,000	73	26	3.8
Alpha-1 antitrypsin	54,000	87.5	12	4.8
Ceruloplasmin	135,000	89	8	4.4
C-reactive protein	21,000	100	0	6.4
Fibrinogen	341,000	97	2.5	5.5
Haptaglobin	86,000		16.5	4.1

Synthesis and turnover:

The acute phase reactants are mainly synthesized in the liver, which is also the main site of their destruction (Cooper and ward, 1979).
It was suggested that trauma leads to the release of substances from the damaged cells, which stimulate leucocytes to produce a series of polypeptides including "leucocyte endogenous mediators (LEM)" and Endogenous pyrogens (EP)", which in turn have a variety of effects on different tissues and organs. An important effect on the liver is to promote increased synthesis of the acute phase proteins, this increased synthesis apparently results from an increased number of synthesizing hepatocytes (Colley et al., 1983).

The estimated half-life of the proteins vary according to type-particular protein, and the techniques used. It ranges between 2-6 days for Haptoglobin, fibrinogen, and ceruloplasmin, 19 days for serum albumin, and 5 days for alpha-1 acid glycoprotein (Cooper and Ward, 1979).

Normal levels:

The various levels of acute phase proteins are summerised in table II (Bienvenu et al., 1984).

Protein	Normal range (adult) 91L	Mean in newborn 91L
C-reactive protein	Traces	Traces
Alpha-1 acid glycoprotin	0.4-0.8	0.18
Haptoglobin	0.6-1.6	0.20
Alpha-1 antitrypsin	2-3.5	2
Alpha-1 chymotryspin	0.3-0.6	0.01
Ceruloplasmin	0.3-0.5	0.15

Biological function:

Several authors postulated that, plasma glycoproteins are involved in the healing of wounds and tissue repair by providing material of both carbohydrate and protein moieties. Histo chemical, chemical, and immunological evidence suggested that sialoglycoproteins become attached to the surface of tumour cells, bringing about tolerance of the host organism to cellular antigens of the tumour. It was emphasized that cells of inflammed and wounded areas share with cancer cells the capacity of stimulating the synthesis of some of the acute phase reactants, particularily rich in carbohydrates as, Alpha-1 acid glycoprotein, Haptoglobin, and Alpha-1 antitrypsin, which return to nromal levels after injury is healed (Koj, 1974). The biological significance of elevated serum acute phase proteins in malignancy is unknown. Their elevations appear to be associated with suppression of cellular immunity (Baskies et al., 1980).

Baskies et al., (1980) reported a correlation between elevated levels of serum Haptoglobin and Alpha-1 acid glycoprotein, and decreased lymphocytic reactivity to phytohem

agglutinin in vitro, and delayed hypersensitivity to dinitro chlorobenzene in vivo.

Phytohemagglutinin is a hemagglutinin dervied from plants, which is capable of inducing lymphoblast transformation and mitosis of both T and B cells in man.

Clinical Significance:

The hepatic synthesis of acute phase proteins appears to be triggered by injury, with the consequent release of constituents of damaged tissue, that participate in the inflammatory process. It is presumed that acute phase proteins participate in some way in the process of inflammation, and tissue repair (Kushner et al., 1981).

Edwards in (1982) stated that some of the glycoproteins of acute phase C_3, Haptoglobin, transferin, and ceruloplasmin, have defense related functions, others seem to participate in phenomena like detoxification, promotion of phagocytosis, woud healing, and prevention of tissue injury by lysosomal enzymes.

Studies of acute phase reactants are limited at present time for diagnositc and prognostic assessments, and in therapy of inborn error of deficiencies of these proteins for example are afibrinogenemia and alpha-1 antitrypsin deficiency (Koj, 1974).

Acute phase reactants in various diseases:

(1) Inflammatory diseases:

It has been suggested that measurement of these proteins, can be used to confirm the presence of infection (Colley et al., 1983).

Bacterial infections evoke marked elevation of all acute phase proteins (Cooper and Ward, 1979). When the acute phase reactants are present in significant amounts, the likelihood of survival is very good. When low levels of acute phase reactants are present, death from infection is likely (Philip, 1979).

The changes in acute phase protein response persist as long as the inflammatory process remains active. Thus, in chronic infections or in connective tissue disorders, the acute phase reactants remain elevated for months or years (Cooper and Ward, 1979).

In the majority of infections the antibiotic therapy can by stopped soon after the return of the acute phase reactants to normal levels (Koj, 1974).

Sann et al., (1984) have confirmed that several proteins are helpful, not only in diagnosis of infection, but also in following the course of illness. When sepsis or meningitis is proved, acute phase proteins can be used to document response to therapy, and deciding its duration.

It is possible that, duration of antibiotic therapy could be modified according to the objective data provided by the acute phase proteins. Other acute phase proteins seem

to respond as a negative reactant i.e their levels fall with inflammation, and increase with recovery e.g. prealbumin and transferrin (Koj, 1974).

(ii) Following surgical trauma:

The acute phase reactants, C-reactive protein, Antichymotrypsin, and Alpha-1 acid glycoprotein rise within 6 hours of surgical incision, and reach peak levels by the second post-operative day. In the uncomplicated cases, they begin to fall by the third day, Failure to fall, or a secondary rise indicate infection or other post-operative complications (Cooper and Ward, 1979).

(iii) In cancer:

The general pattern of response of acute phase reactant proteins to an increasing tumour load, is an elevation of these glycoproteins.
All investigators agree that the levels of acute phase proteins have no place as a diagnostic aid in primary cancer. Their applied role, seem to lie in the monitoring of established cancer. In breast cancer, serum levels of Alpha-1 acid glycoprotein, Alpha-1 antitrypsin, Haptoglobin and C_3, were found to be elevated in women with stage IV as compared to women with stage I or II or controls. Thus, measurement of acute phase proteins are useful in staging the cancer and in following the dissemeinated lesions (Thompson et al., 1983).

Similar findings were reported in a number of other tumours including carcinoma of the bowel, prostate, bladder,