REVIEW OF LITERATURE
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All human beings are susceptible to infections irrespective of their age, sex, race. However, few are more exposed to infection than others, especially newborns. The immunoglobulins are a family of proteins which may be identified in the plasma or serum by immunochemical methods. The main components have been identified (Franklin, 1962), viz. IgG, IgA, IgM, IgD and IgE.

Infants depend primarily upon placentally transferred immunity for protection of infection in early life. Data collected subsequently revealed that, cellular immunity also plays a significant role in host defense. Both humoral and cellular immune mechanisms impact resistance to traumatic experiences just after birth.

General Immune Response -

Immunogen entering the body excites two types of reactions (i) initial non-specific immune reaction (NSIR) comprising an inflammatory response with subsequent phagocytosis, and (ii) specific immune reaction (SIR) comprising antibody dependent and cell mediated reactions.
Antigen - Host -
- Non-specific immune reaction (NSIR)
- Specific immune reaction (SIR).

The NSIR is mediated by phagocytic cells including those of mononuclear phagocytic system (MPS), polymorpho-nuclear leucocytes (PMN), eosinophils and mediator cells including mast cells, basophils and platelets.

The specific immune reaction as a whole is dependent upon the nature of the immunogen/antigen. The site of response is lymphnodes and spleen and the mediators include T and B lymphocytes, killer cells, natural killer cells and macrophages. The complement and Kallikrein systems assist the antibody dependent reactions mediated by B-cells.

The chief function of lymphocyte is generation of immunity by a complex phenomenon, culminating in the synthesis of specific immunoglobulin (antibody) and establishment of cellular immunity.

The antibody activity of serum and other body secretions is associated with a heterogenous group of proteins, collectively known as immunoglobulins (Ig). These proteins are also known as gamma globulins because of their relative electrophoretic mobility. Many antibodies migrate more rapidly than gamma globulins and some molecules unrelated to antibodies, may also migrate with the electrophoretic mobility of gamma globulins. For these reasons
the term "Immunoglobulins" and symbol "Ig" or "" has been suggested to designate the family of molecules with antibody activity (Committee of Nomenclature of Human Immunoglobulin - Bull. WHO, 1964, Fahey, 1965).

Gamma globulins, by virtue of their antibody activity, play a significant role in resistance of infection. However, antibody alone may not be sufficient to resist the infection since the ultimate destination or localization of invading organisms depends upon the interaction of antibody and defence mechanism. Antibody potentiates the migration of bacteria by phagocytes (Samuel et al, 1970).

During health, fairly stable levels of immunoglobulins are maintained in the plasma due to the state of equilibrium between the rate of synthesis and catabolism. Levels are subject to vary due to wide spectrum of antigenic stimuli. The variations would also be expected due to difference in environmental, racial and genetic factors and socio-economic status.

In a developing country like India, where a relatively higher incidence of subclinical infection is likely to be encountered, the healthy population would reveal some diversity in the levels of immunoglobulins of normal population as already established in Western literature.

There are three main types of immunoglobulins with antibody activity, which are immunoglobulin G (IgG),
Immunoglobulin M (IgM), and Immunoglobulin A (IgA).
Recently, two more proteins with immuno-chemical characteristics related to these immunoglobulins, Immunoglobulin D (IgD) and Immunoglobulin E (IgE) have been detected.

Despite the tremendous heterogenicity, all the immunoglobulins share structural similarity. All consist of a basic sub-unit composed of four polypeptide chains, held together by disulphide bonds.

According to Eldaman and Poulik (1961) gamma globulins could be split into two components by mild reduction with thiols in the presence of urea. Each of the two components consisted of polypeptides - 1. The heavy chain (molecular weight 50,000) and 2. light chain (molecular weight 20,000). Authors further observed that about 75% of an IgG molecule was made up of heavy chain while the remaining 25% consisted of light chains.

Kunkel and Grey (1964) discovered the sub-class of IgG, viz. (IgG₁, G₂, G₃ and G₄).

Rowe and Fahey (1965) discovered the fourth class of immunoglobulin viz. IgD from an atypical myeloma proteins which did not react with any of the known anti IgG anti IgA or anti IgM sera. Kunkel and Prendergast (1966) discovered the sub-class of IgA, while Ishizaka and Hornbook (1966)
discovered the fifth class of immunoglobulins IgE during their study of reaginic antibodies.

Hong et al (1972) classified the immunoglobulins in five major classes (IgG, IgM, IgA, IgD and IgE) on the basis of their general property, structural differences of their heavy chains including the amino acid sequence and length of the polypeptide chain. He summarized the chemical, biological and metabolic characteristics of immunoglobulins which are included in the table given.

**Immunoglobulin G (IgG)**

IgG is the major immunoglobulin and constitutes about 3/4th of total gamma-globulin. IgG has a sedimentation constant of 7S and contains about 90% of acquired antibodies. It has been observed that the concentration of gammaglobulin in the plasma of newborn infant is equal to or greater than that of their mothers because of selective transfer across the placenta. After birth the level is minimum between 3-6 months of age. The concentration then rises again to reach adult levels between first and second year of life. Synthesis of immunoglobulin G occurs at 11th week of gestation (Cocchi et al, 1969 and McCraken et al, 1971). It has a molecular weight of 150,000 daltons. IgG is the only immunoglobulin that crosses the placenta and thereby provides maternal antibodies to neonate (Fahey, 1965). Mean serum concentration of IgG in cord blood of a newborn baby is usually in the range of 740-1650 mg% (Hardy et al, 1969)
### TABLE

Biological and metabolic characteristics of Immunoglobulins modified from Byung, H. Park, Robert, A., Good (1974) and Hong et al (1972).

<table>
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<tr>
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<th>IgG</th>
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<td>Molecular weight</td>
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<td>160,000</td>
<td>370,000</td>
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<tr>
<td>Half life (days)</td>
<td>25 - 35</td>
<td>9 - 11</td>
<td>6 - 8</td>
<td>2 - 3</td>
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<tr>
<td>Production (mg/kg/day)</td>
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<td>5 - 8</td>
<td>8 - 10</td>
<td>0.4</td>
<td>-</td>
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<tr>
<td>S. concentration (mg/100 ml)</td>
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<td>50 - 200</td>
<td>60 - 420</td>
<td>3</td>
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<td>Transplacental passage</td>
<td>+</td>
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<td>Complement fixation</td>
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<td>Secreted by mucous surface</td>
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<td>Polymer formation</td>
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<td>Blocking antigen</td>
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which consists mostly of maternal antibodies and falls to a level of about 200 – 600 mg% by about six months of age. As the infant is exposed to antigenic environment IgG levels gradually start increasing reaching adult levels (i.e. 800 - 1200 mg%) by about four years of age.

On the basis of antigenic determinants within the heavy chain of IgG, four isotypic classes of IgG molecules have been identified in the normal serum. These are IgG1 (66%), IgG2 (23%), IgG3 (7%), IgG4 (4%). Following are the mean serum IgG levels in cord blood as given by different authors: 740 - 1650 mg% (Hardy et al, 1969), 348 - 2000 mg% (Evans et al, 1971), 612 - 654 mg% (Malik et al, 1977), 860.68 - 1312.13 mg% (Sethi et al, 1980), 1402 ± 132.3 mg% (Sharma et al, 1986) and 1120 - 1692 mg% (Kolhatkar et al, 1987).

**Immunoglobulin A (IgA)** -

IgA is the next most abundant immunoglobulin in serum. IgA globulin has a sedimentation constant between 69 and 135. It has been shown to be absent from the plasma of newborn infant as it does not cross the placenta and its synthesis begins at about the 2nd to the 4th week of life. Not much is known about the antibody content of this fraction but recent studies shows that some of the skin sensitizing antibodies in certain allergic individuals and Brucella abortus and diphtheria antibodies may belong to
this fraction. The class IgA comprises about 10 percent of the gamma globulin in human serum. IgA class can be sub-divided into two separate systems of Immunoglobulins. One of these provides IgA antibodies for internal secretions synthesized by non-mucosal lymphoid tissue. The other system of IgA antibodies are found in external secretions. IgA of external secretions in most parts is not derived from blood but is produced locally by plasma cells. IgA synthesis is virtually undetectable in the fetus and do not become substantial for several months after birth. Serum levels of IgA is 0 - 3.9 mg% (Malik et al, 1977) at birth and gradually increases to about 25 - 75 mg% by two years of age. Adult levels 200 to 300 mg% are reached in adolescence (Tomasi et al, 1968 and Soloman et al, 1973). Secretory IgA have antibody activity against a variety of viruses, bacteria (Clancy and Bienestock, 1976). Molecular weight of serum IgA is 160,000 daltons and of secretory IgA is 370,000 daltons. Following are the levels of serum IgA in cord blood as estimated by different workers: 0 - 46 mg% (Evans et al, 1971), 0 - 30.9 mg% (Malik et al, 1977); 9.12 ± 10.04 mg% (Kaur et al, 1979); 25.4 ± 5 mg% (Hariharan et al, 1984).

**Immunoglobulin M (IgM)** -

IgM is the largest of the polymeric immunoglobulins, usually being a pentamer of the H₂ L₂ structure with one J chain. IgM immunoglobulin has a sedimentation constant of
19S, this fraction, like IgA globulin is incapable of crossing the placenta. But its synthesis can occur at a slow rate in the foetus. After birth, the rate of synthesis increases rapidly and it has been reported that adult level may be reached by the 9th month of age. Recent work has shown that the newborn infants are by no means immunologically incompetent as it was once thought to be. Molecular weight of IgM is 900,000 daltons. IgM is also known as macro-globulin due to its high molecular weight. IgM is produced in the primary response to antigenic challenge. IgM is the main immunoglobulin produced by the fetus and while the amount formed is usually small when there is fetal infection, substantial IgM response may occur. Serum concentration of IgM in a newborn is about 1.6 to 31 mg% (Hardy et al, 1969) which rapidly increases to adult level of 50 - 150 mg% by about 1 year of age. The IgM level in serum is between 5 and 10 percent of the total antibody protein. Following are the cord serum levels of IgM as reported by different workers - 1.6 to 31 mg% (Hardy et al, 1969), 0 - 25 mg% (Khan et al, 1974), 0 - 20.8 mg% (Malik et al, 1977), 9.12 ± 10.04 mg% (Kaur et al, 1979), 22.8 - 84.4 mg% (Hariharan et al, 1984) and 12.1 ± 13.5 mg% (Sharma et al, 1986).

Immunoglobulin D (IgD) -

IgD is found in very low concentration in the serum, 0.3 to 40 mg% (Rowe and Fahey, 1965). IgD was
discovered by Rowe and Fahey having a molecular weight of 180,000 daltons and found mainly in the intravascular space and on resting B cells as a cell surface immunoglobulin. IgD comprises about 3 mg percent of normal serum immunoglobulins.

**Immunoglobulin E (IgE)**

IgE is also known as reagenic antibody, mediates acute, sometime life threatening allergic reactions in atopic patients. It has a molecular weight of 190,000 daltons and binds to basophils and mast cells when a specific antigen combines with the antigen binding site on IgE. The serum concentration of IgE is in the range of 0.01 to 0.07 mg% with a mean of 0.03 mg% (Bennich et al, 1971).

**Human Complement C₃**

This complement component is present in human serum in a concentration of approximately 1.2 mg/ml which is by far the largest amount of any complement in serum (Lundh, 1964; West et al, 1964; Klemperer et al, 1965; Kohler and Muller-Eberhard, 1967). Its sedimentation coefficient is 9.5 'S' and the molecular weight is estimated to be approximately 240,000. It is readily demonstrated by immuno-electrophoresis of whole human serum, the corresponding precipitin being located in the B-globulin region and partially within the transferrin arc (Muller-Eberhard et al, 1960).
Complement plays an integral role in host defence against infection. The deficiency of complement components in neonatal serum has been implicated to be cause of defective opsonic activity and chemotactic activity (Forman et al, 1969). The synthesis of C₃ complement takes place in fetal liver (Miller, M.E., 1971) and no transplacental transfer has been documented (Miller, 1978). Out of all the complement components C₃ is present in highest concentration in adult and neonatal serum. Following are the values of mean serum complement C₃ in cord blood as given by various authors: 124.72 ± 44.62 mg% (Kaur et al, 1979), 90 ± 18 mg% (Shapiro et al, 1981), 51.4 ± 14.94 mg% (Tandon et al, 1984).

**Immunoglobulins in Neonates**

Susceptibility of the newborns to various infections has been known for a long time. This is particularly the case in premature and small for date infants where infection leads to increased rate of mortality and morbidity. Maternally transmitted immunoglobulin IgG is the main stay of the humoral immunity in postnatal period. Antibodies produced by B-cells are located in the globulin fraction of the serum (Tisellus and Kabat, 1939) and are called immunoglobulins.

Immunoglobulins in the serum can be measured by many methods. Single radial immuno-diffusion method has been found to be simple, easily performed and in wide use especially due to its easy availability in the market
Lymphocytes with IgM, IgG, IgA surface receptors have been demonstrated by immunofluorescence in the peripheral blood, liver spleen, and bone marrow at 11½ weeks of gestation. Normally only IgG can cross the placenta. The presence of IgM and IgA in the cord and newborn sera is the result of active synthesis by the fetus or because of maternal bleeding into the fetal circulation.

Thus we see that a normal full term healthy infant at birth has an incompletely developed immunological system that is why, is more prone to develop infections. Both prenatal and postnatal infections alter the immunological status of the newborns. The immunological status of the newborn is further compromised in low birth weight infants. Hyperbilirubinemia of newborn also plays an adverse effect on the immunological status of the newborn. Following is a brief review of the literature regarding the immunological profile in various neonatal disorders and normal infants.

**Immunological profile or Normal healthy full term babies**

Babies with birth weight of more than 2.5 kg, more than 37 weeks of gestational age, without any infection born as a result of normal vaginal delivery have been kept in this group.
IgG -

Synthesis of Immunoglobulin IgG occurs at 11 weeks of gestation (Cocchi et al, 1969 and McCraken et al, 1971). Mainly IgG lies in the maternal blood and is selectively transported through placenta to the fetus. This occurs mainly in III trimester, hence infants born before 34 weeks of gestation have deficiency of IgG. Rate of transfer of IgG depends upon maternal IgG levels as well as the age and function of placenta (Chandra, 1975). A small amount of IgG is however, synthesised in utero by the fetus (Gotoff, 1974). Allansmith et al (1968) have reported higher cord blood IgG levels than maternal blood. These findings were confirmed by Chandra et al (1970). A linear relationship between IgG levels and gestational age was suggested by Evans et al (1971). Raghvan et al (1976) also showed a correlation between the levels of IgG and the gestational age of the neonate. Malik et al (1977) reported higher IgG levels in the full term neonate than the corresponding mother. Similar findings were obtained by Mahambare et al (1978), they also supported the fact that the levels of IgG were directly proportional to the gestational age and not to the birth weight. The levels of serum IgG were directly correlated with the birth weight, and period of gestation (Kaur et al, 1979). Sethi et al (1980) showed a linear correlation of serum IgG levels with gestational age. In a study conducted by Hariharan et al (1984), it was concluded that the IgG levels were high, at birth and in agreement with values
reported by Western and Indian workers. No correlation was seen between maternal and cord serum IgG levels, the cord serum IgG levels were significantly correlated with gestational age (Tandon et al, 1985). Sharma et al (1986) reported IgG level in cord blood to be 1402.31 ± 132.31 mg/100 ml, which is in agreement with various workers. Kolhatkar et al (1987) reported that serum IgG levels of Indian infants were appreciably higher than their Western counterparts at all ages.

**IgM**

The immunoglobulin IgM can be produced by the fetus by 10½ weeks of gestation (Gottoff, 1974) but the levels remains very low at birth (Steihm et al, 1966). Allansmith et al (1968) reported that level of IgM remains constant for the first 5 days after birth, and then increases rapidly for 2 days. Newborn develop 50% level of the adult values of IgM by the end of four months of age and adult levels are attained by the age of 1 to 2 years (Allansmith et al, 1968). Some of the newborns were having high levels than normal infants which was attributed to maternal bleeding into fetal circulation (Sever et al, 1969). Levels of IgM are not related to sex and infants having lower levels of IgM are at a risk of death (Hardy et al, 1969). IgM levels can be determined by a simple radial diffusion method (Khan et al, 1969). Prasad et al,
(1971) observed lower levels of IgM as compared to the reported figures. Evans et al (1971) reported similar levels of IgM among multiple-birth newborns corresponding to those of single infant of same gestational age. Raghvan et al (1976) reported a higher level of IgM in the Indian population as compared to the reports from the west. IgM levels were low and had no relation with the gestational age and birth weight indicating absence of placental transfer and negligible synthesis by the fetus (Mahambare et al, 1978). Higher serum IgM levels in cord blood as compared to Western world, were reported by Hariharan et al, (1984). Sharma et al (1986) reported no significant relationship of cord blood IgM with birth weight and gestational age. A high value of serum IgM was observed in the post-mature babies by Goel et al (1987). Low serum IgM values at birth were reported by Kolhatkar et al (1987) and they increase as the age advances.

Complement $C_3$ -

Not much work has been published regarding the level of complement in the newborn babies. Subnormal complement activity in cord blood was reported in 1927 by Larrier et al. In 1964, Lundh et al reported that complement $C_3$ was present in neonates in a concentration of 1.2 mg/ml. Similar findings were confirmed by Kohler and Muller-Eberhard (1967). They also reported that $C_3$
is the fraction of complement system present in largest amount in the blood. All components except C₃ increased in concentration during the first four days of life (Ballow et al., 1974). In man, synthesis of complement can occur as early as the eighth week of gestation and precedes the appearance of immunoglobulins (Colten et al., 1974). Drew and Arroyave (1978) found a statistically significant correlation between increasing birth weight or gestational age and increasing serum concentration of C₃ fraction.

Complement synthesis begins early in autogeny and precedes immunoglobulin synthesis. It starts at 8th week of intra-uterine life and is established by 11 - 14 weeks. Complement do not cross placenta and normal values of C₃ were ranging between 60 - 200 mg% (Kaur et al., 1979). Shapiro et al (1981) reported values of C₃ in cord blood of healthy neonates of about 90 mg%. When the birth weight was controlled the correlation between the cord serum C₃ levels and gestation (P > 0.05) became insignificant. Similarly, when gestational age was controlled the correlation between the birth weight and cord serum C₃ levels became insignificant (Tandon et al., 1984). Singh et al (1986) reported that break down product of C₃ were not detected in healthy neonates.
Immunological profile of low birth weight babies -

Babies with birth weight of less than 2.5 kg irrespective of the period of gestation, born by normal vaginal delivery, have been included in this group. The group includes premature babies having weight appropriate for gestational age, as well as small for date newborns. Small for date babies are those who weigh less than expected for the gestational age, the weight falling below the 10th percentile for the period of gestation or 2 standard deviation below the mean weight.

Naeye (1966), described 2 groups of small for date babies on the basis of pathological observations. The first group is of malnourished small for date babies, occurring as a result of foetal malnutrition during the later part of gestation. These infants show diminished amount of cytoplasm in the cells. The second group also called hypoplastic group, is attributed to intra-uterine infections and genetic and chromosomal disorders. This group contains normal amount of cytoplasm in the cells but cells are reduced in number.

IgG -

Hobbs and Davis (1967) measured levels of Immunoglobulins in a group of small for dates (prematures) in the first week of life and observed that there is a linear relation between the level of IgG and gestational age.
All prematures born before 32 weeks gestation had IgG less than 400 mg%.

Yeung and Hobbs (1968) observed that there was a significant decrease in serum IgG levels in both small for date and premature babies as compared to full term infants. They observed a mean serum IgG levels in small for date infants (40, 38½ and 37 weeks of gestation) to be 626, 578 and 512 mg% respectively, as compared to values of 1100, 879 and 757 mg% observed in control group of cases of similar gestational age group. The serum IgG levels in AGA group of infants showed a linear correlation with increasing gestational age. The lower levels of IgG can be due to the placental insufficiency.

Rothberg (1969) observed that serum IgG levels have got a definite linear relationship with the increase in the weight of the premature infants.

Evans et al (1971) observed that serum IgG levels showed a definite increase with the increase in weight of the premature infants. With decreasing gestational age the median values of IgG declined. At 40 wks, 35 wks, 31 wks and 27 wks the IgG values were 1088, 850, 595 and 430 mg% respectively.

Hyvarinen et al (1973) did not observe a significant decrease in the levels of serum IgG in small for date infants, only 2 of the 8 studied showing a decreased levels of this class of immunoglobulin.
In 1975, Chandra studied the immunological status in 26 normal full term and 26 S.F.D. infants and observed that the serum IgG levels have got a linear relationship with the gestational age. The follow-up of 10 S.F.D. babies showed that not only serum IgG levels were low but the subsequent drop in the IgG levels was also much severe in S.F.D. as compared to the normal full term infants.

Raghvan et al (1976) studied immunoglobulin IgG in sixteen healthy premature neonates and compared the pattern obtained in fifteen healthy full term neonates. They reported IgG values of $170.8 \pm 99.1$ I.U./ml in prematures which were significantly lower when compared to the values of $253.6 \pm 137.6$ I.U./ml obtained in full term ($P \leq 0.025$). The levels of IgG in cord sera of premature neonates showed a direct correlation with the birth weight ($P \leq 0.01$).

Pre-term babies showed significantly low levels of IgG, in a study conducted by Meharban Singh (1978). The neonates with severe IUGR and pre-term babies had significantly lower levels of IgG ($P \leq 0.01$). The values of immunoglobulin IgG in IUGR were $92.05 \pm 17.03$ I.U./ml and in preterms were $86.49 \pm 30.30$ as compared to the normal neonates in whom the values were $138.91 \pm 34.75$. The pre-term babies had significantly low levels of IgG in the cord blood because materno-fetal transfer of immunoglobulins occurs during third trimester of pregnancy.
Hobbs and Davis (1967) gave a direct relationship between the cord blood IgG and gestational age, similar results were obtained in the study by Singh et al (1978).

Kaur et al (1979) reported in her study that the levels of IgG were directly correlated with the birth weight and period of gestation. Serum IgG levels in pre-term, S.F.D. and controls were 829.66, 1142.06 and 1478.5 mg% respectively. It was observed that the values obtained in both premature and SFD babies were statistically significant from those observed in the control group of babies ($P \leq 0.001$). This was in agreement with the results concluded by Chandra et al (1976). Raghvan et al (1976) and Mahambare et al (1978). Sethi et al (1980) in a study of 20 L.B.W. newborns (14 SFD and 6 AGA), observed a significant decrease in serum IgG levels of both SFD and AGA infants as compared to control ($P \leq 0.001$). This decrease was more pronounced in S.F.D. having prematurity as well. The findings also showed a linear correlation between IgG levels and gestational age. The mean serum IgG levels of six premature SFD infants (478.2 mg%) was much less as compared to that of premature AGA infants of same gestational age (687.35 mg%) indicating placental pathology commonly observed in S.F.D. infants.

Shapiro et al (1981) however in their study reported values contrary to those observed by other workers in the field. They studied 28 term newborns of
whom 17 were SGA and 11 were A.G.A. They observed that there was no significant difference between the serum IgG values in both the group ($P \geq 0.005$) values being 1363 and 1461 mg% in A.G.A. and S.G.A. respectively.

Tandon et al (1984) reported that the cord serum IgG levels were significantly lower in pre-term babies ($712 \pm 207.2$ mg%) compared to full term AGA ($1450 \pm 478.6$ mg%) and full term - IUGR babies ($1586 \pm 538.1$ mg%). The cord serum IgG levels were significantly correlated with gestational age.

Khatua et al (1984) conducted a study consisting of 20 control, 18 term SFD and 12 premature infants and observed IgG levels of $1040.75 \pm 146.56$ mg%, $888.05 \pm 270.4$ mg% and $728.38 \pm 120.12$ mg% respectively. On statistical evaluation the workers observed a significant difference in the IgG values of premature and S.F.D. as compared to the control group of cases ($P \leq 0.001$ and $P \leq 0.05$).

Sharma et al conducted a study in 1986 and observed that the mean IgG levels in controls, prematures and F.T. IUGR were $1402.31 \pm 132.31$, $1267.3 \pm 84.0$, and $1422.0 \pm 102.0$. The mean IgG concentration in pre-terms was significantly ($P \leq 0.001$) lower than full term newborns.

In a study of S.F.D. done by Bhatia et al (1987), significantly lower cord serum IgG levels were found in
premature babies irrespective of their intra-uterine growth status.

Goel et al (1987) conducted a comparative study of immunological status in pre-term, term and post-term infants and observed the mean IgG level in the three groups was 821.43, 1179.45 and 1328.54 mg% respectively. The difference in the values between term and pre-term group was significant (P < 0.01).

IgM -

Yeung and Hobbs (1968) in a study of small for date and AGA infants observed raised IgM levels in 12 out of 28 small for date babies. As increase in the serum IgM level in newborns is known to be the result of intra-uterine infection, the authors suggested that intra-uterine infection might have led to the fetal malnutrition, or alternatively abnormal placentae of the S.F.D. babies may have permitted the entry of organisms in the fetus.

Rothberg (1969) observed in his study that serum IgM levels were independent of the weight and gestational age of the newborn. Hardy et al (1969) observed no significant difference in the serum IgM levels in relation to the weight and sex of the newborn babies.
Evans et al (1971) in an immunological study of premature infants observed that IgM was not detected in cord sera of 37-75% premature infants with standard plates. However, 64 infants showed IgM values 15 mg per 100 ml or more with Low Level Test plates with a range of 1.4 to 27.0 mg per 100 ml. IgM levels did not show any correlation with the length of gestation or birth weight.

Prasad et al (1971) also conducted a study on immunoglobulin levels in twenty four preterms, twenty full term neonates, fifteen infected infants and found that level of IgM in cord blood in premature babies was in the range of 2.8 to 11.6 mg% with a mean of 6.66 ± 3.6 mg%.

Chandra et al (1975) studied the serum IgM in 26 normal and 26 S.F.D. infants and observed findings similar to other workers i.e. serum IgM levels were having no relationship to birth weight and gestational age.

Raghvan et al (1976) studied serum IgM in sixteen healthy premature and fifteen full term neonates and observed no statistically significant difference in the IgM values of preterms and full terms. Though IgM was detected in all the infants except one premature. Mean level of IgM in the cord blood in preterms was 10.04 ± 7.51 mg% with a range of 0 to 24.47 mg%.
Mahambare et al (1978) performed a study on cord blood in 50 cases (forty four babies were full term and 6 were prematures) and found that IgM concentration in the cord is not affected either by the gestational age or the birth weight. No significant difference between the two weight groups of full term babies \( t = 0.943, P = \text{not significant} \) was observed. In premature babies also cord IgM levels were very low and no difference in the levels with different gestational age was seen.

Singh et al (1978) assessed the immunoglobulin IgM, IgG and IgA in 20 F.T. and 12 prematures and 24 IUGR newborns. They observed no significant difference in the value of cord IgM in the different groups. Cord serum IgM values observed in IUGR, premature and controls were \( 20.00 \pm 19.35 \), \( 14.75 \pm 14.65 \) and \( 18.71 \pm 12.75 \) I.U./ml respectively.

Kaur et al (1979) conducted a study of pre-term S.F.D. and F.T. babies and assessment of humoral immunity was done by single raidal diffusion technique. They observed that IgM was present in the cord blood of only some of the babies in all the three categories at birth that is in six pre-term (40%), two S.F.D. (13%) and ten controls (50%). Cord IgM level was 5.13, 1.76 and 9.12 mg% respectively. Further, they reported that IgM levels are not dependent on the birth weight of the newborn babies.
Shapiro et al (1981) conducted a study of 28 term newborns, of whom 17 were SGA and 11 AGA. They found cord IgM levels of less than 20 mg/ml and observed no significant difference (P > 0.05) between the serum IgM levels of the two groups. Placental histology did not reveal any placental infection in SGA patients.

Sharma et al (1986) studied the cord blood of 100 newborns by single radial immuno-diffusion technique and observed that mean serum IgM levels of 11.58 ± 12.58 mg/100 ml. IgM did not show any significant correlation with birth weight and gestational age. The levels of IgM in pre-term, borderline pre-term and full terms were 7.4 ± 2.9, 8.2 ± 5.2 and 12.1 ± 13.5 mg/100 ml respectively.

Bhatia et al (1987) in a study of hundred twelve live born singleton babies observed that serum IgM levels were not having significant difference in the various groups viz. LBW babies, F.T. A.G.A. babies and F.T. IUGR babies.

Goel et al (1987) estimated serum IgM and other immunoglobulins by simple radial immuno-diffusion technique developed by Mancini et al (1965), in the cord blood of 72 normal newborns. Out of these 72 cases there were 28 premature, 32 full term and 12 post-mature neonates. IgM was observed in only 25% of the total cases in which post-mature infants had maximum percentage (66.66%).
The mean serum IgM values in these three sub-groups were 39.40, 44.25 and 45.71 mg% respectively as compared to 118.25 mg% in 12 adult specimens showing significant relationship (P < 0.01).

Complement C₃ -

Ballow et al (1974) reported that all components except C₃ increased in concentration compared to maternal levels during the first four days of life. Pre-term infants had less whole complement activity and lower complement concentrations than full term infants. Drew and Arroyave (1978) found a statistically significant correlation between increasing birth weight or gestational age and increasing serum concentrations of complement specially C₃. Concentrations of C₃ have been 60% to 100% of adult concentrations in term infants and some what less in pre-term infants. Younger gestational age has been correlated with lower levels of complement C₃.

Jagadeesan and Reddy (1978) studied levels of serum complement in 54 newborns out of which 25 were S.F.D. The mean serum complement levels in infants weighing more than 2500 gm were 29.4 U/ml. It is observed that there was no significant difference in the complement levels between the S.F.D. group with different birth weights. The serum values in S.F.D. having weight between 2000 gm to 2500 gms were in the range of 25.58 to 29.6 units/ml.
In this study complement activity did not seem to be altered in S.F.D. infants.

Kaur et al (1979) studied the complement activity in pre-term, S.F.D. and term babies and observed that the levels of complement C₃ were lower in the pre-term and S.F.D. babies as compared to that observed in term babies at birth. They also observed that pre-term babies have lower levels of complement in proportion to their immaturity. They opined that complement components do not cross the placenta and further communicated that preterm infants have a defective opsonic activity to all organism or antigens whereas the term newborn serum apparently has decreased opsonic activity only to certain organisms, primarily gram negative organisms.

Shapiro et al (1981) studied 28 term newborns of whom 17 were SGA and 11 AGA and reported that mean C₃ concentration in SGA group was significantly lower (P ≤ 0.02) than in the AGA group. C₃ concentration in AGA and SGA infants was 90 mg% and 75 mg% respectively.

Tandon et al (1984) reported that cord serum C₃ levels of 50 low birth weight babies was significantly lower in pre-term when compared to term AGA and term IUGR babies. However, C₃ level was not significantly different between term AGA and term IUGR babies. No correlation could be seen between C₃ levels and birth weight.
The mean levels of complement C₃ in term AGA, pre-terms and term IUGR was 51.5 ± 14.94, 33.8 ± 11.18 and 47.5 ± 19.75 respectively. The cord C₃ level was found to be significantly correlated with the gestational age (Fireman et al, 1969; Steihm et al, 1975; Jagadeesan et al, 1978).

Bhatia et al (1987) reported significantly lower cord serum C₃ levels in pre-term babies irrespective of their intra-uterine growth status. C₃ level was also reduced in F.T. IUGR low birth weight babies when compared to F.T. AGA controls. Both gestational age and birth weight was found to be independent of the complement status.

**IMMUNOLOGICAL PROFILE IN HYPERBILIRUBINEMIA CASES**

Although neonatal jaundice is a common condition and effect of unconjugated bilirubin on various body tissues is well documented yet not many studies have been done in the past, to observe the correlation of hyperbilirubinemia on the humoral immune status of the neonates. The results of these studies point towards a depressed state of immune responsiveness of the newborn having hyperbilirubinemia.

**IgG -**

Nejelda (1967) observed the immune status of newborn babies with erythroblastosis fetalis and reported that the levels of serum gammaglobulins as a whole were
significantly decreased in these babies as compared to the healthy neonates. The suppression of antibody response was thought to be due to the impairment in the development of the cells involved in immune system, and because of the toxic effect of hyperbilirubinemia on the reticuloendothelial system.

Ansaldi et al (1968) conducted a study to find out the effect of hyperbilirubinemia on the humoral immune response and reported no significant change in the levels of immunoglobulins IgG in neonates with bilirubin levels above 16 mg% when compared to normal healthy controls.

Nejelda (1970) in another study done later reported that high serum bilirubin levels suppressed the immune response in newborns during the 1st week of life as well as in those infants who were followed up for 1 year.

Mantalenaki et al (1975) evaluated the effect of exchange transfusion on the serum immunoglobulin levels in the neonates with hyperbilirubinemia and found variable effects on different immunoglobulins. Exchange transfusion had a prolonged inhibitory effect on the synthesis of serum IgG and IgA. The exact mechanism of this phenomenon was not clear but the levels of all classes of immunoglobulins were same in infants with hyperbilirubinemia not having received exchange transfusion and in controls.
Several explanations have been given to explain the suppression of the immune response with increasing concentration of bilirubin. Nejelda (1970) and Pleszezynski et al (1975) put forward the hypothesis of the toxic effects of hyperbilirubinemia on the viability of the immunological status of the cells. Pleszezynski et al (1975) on the experimental basis observed that hyperbilirubinemia interferes on same metabolic pathways in the production of immunity viz. damage of the lymphocyte membrane by bilirubin. Hirshchorn and Hirshchorn (1965) and Noir et al (1972) suggested that the detrimental effect on immunity may be due to interaction of increasing bilirubin levels with the lysosomal membrane or due to inhibition of function of mitochondria respectively.

Sethi et al (1989) reported no significant alteration in serum IgG levels as compared to control. Thirty cases of neonatal hyperbilirubinemia were studied. The serum values of IgG in control and hyperbilirubinemia group were $1102.58 \pm 134.43$ and $995.87 \pm 163$ mg% respectively. P value was $\neq 0.05$.

IgM -

Ansaldo and associates (1968) evaluated the effect of bilirubin on humoral immunity and reported slightly lower levels of IgM in neonates with bilirubin levels above 16 mg% when compared to normal healthy infants not having jaundice.
Complement C₃ -

So far there is no study reported in the literature about the effect of bilirubin on the complement system and their components specially C₃.

IMMUNOLOGICAL PROFILE IN CASES OF NEONATAL INFECTIONS

The immune status of a neonate forms the baseline of any study of immune response in man as active immune responses become operative immediately after exposure to the antigenic stimuli from the environment. In this country, these stimuli became operative quite early as an average neonate has a greater chance of an exposure to infection fairly early in life. The low level of immunoglobulins specially IgM at birth makes the neonate more susceptible to gram negative infections.

IgG -

Alford et al (1967) in a study of infected neonates observed no change in the level of serum IgG in the control and the neonatal infection group.

McCraken et al (1969) studied 2600 serum samples. Serum IgG was studied in 88 cord sera with congenital rubella and compared with the values in controls. No significant difference was observed in the values of serum IgG in the control and the study groups.
Similar observations were recorded by Sever (1969) and Chandra et al (1970) in a study of the effects of neonatal infections on the immunological profile.

Prasad et al (1971) studied twenty normal neonates and 15 neonates with acute infections alongwith prematures and observed that there was no significant difference in the mean serum IgG levels in the control and infected neonates, the values of IgG were $444.6 \pm 20.4$ mg% and $479.8 \pm 32.4$ mg% respectively.

Malik et al (1977) in a study of immunoglobulins in the neonates born of mothers suffering from infection during their antenatal period, premature rupture of membrane, toxaemia of pregnancy and malformed full term neonates reported that serum IgG levels were raised in the premature rupture of membrane group as compared to control group, and possibly it was due to the infection in mother leading to increase in the serum IgG levels of the neonates due to passive placental transfer. No significant difference was seen between the serum IgG levels in the controls and the baby born to infected mothers, the values were $253.6 \pm 137.5$ and $243.6 \pm 107.3$ mg% respectively.

Mahambare et al (1978) reported that the mean 8th day serum IgG level in the neonates was slightly lower than the cord level of IgG in the controls. Though it was
not significant \( (t = 1.1, \ P \text{ not significant}) \), it may indicate that the infant had yet out begun to synthesis their own IgG.

Mehta et al (1987) studied immunological profile in 70 septicemic and 40 normal neonates to evaluate its usefulness as a diagnostic and prognostic tool in neonatal septicemia. Serum IgG levels were significantly lower in septicemic neonates. Decreased IgG levels in serum correlated with a poor outcome among septic newborns.

\textbf{IgM -}

Alford et al (1967) evaluated from their study of acutely infected neonates postnatally, that high levels of IgM beginning from the third day after onset of infection.

Sheldon et al (1969) in another study of 57 cases suffering from septicemia observed that serum IgM levels were raised in all the cases, the rise was 1st to appear in newborns with pneumonia.

John L. Sever (1969) reported that IgM immunoglobulin levels are often elevated in infants in association with congenital and perinatal infections.

Hardy et al (1969) reported an increase in the levels of serum IgM in newborns having septicemia as well as in those whose mothers had suffered from respiratory infections during pregnancy.
Prasad et al (1971) observed an appreciable rise in the serum IgM fractions in response to infection. They studied twenty normal and fifteen neonates with acute infections and observed serum IgM values in controls and infection group to be $17.88 \pm 1.77$ mg% and $39.2 \pm 8.36$ mg% respectively.

Blankenship et al (1974) also observed an increase of IgM in 80% of cases and reported a greater increase in viral as compared to the bacterial infections. Further they reported that staphylococci were most antigenic among various bacteria; they studied.

Malik et al (1977) studied the immunological profile of neonates exposed to the risk of perinatal infections. They found that the levels of serum IgM were significantly raised in newborns born to mothers having definite history of acute infection, during pregnancy. The levels of IgM were normal in neonates born after premature rupture of membranes. The failure of IgM levels to increase in the neonates born after premature rupture of membranes was explained by the authors to be due to the failure of the infective stimulus to reach the fetal immune system. The values of IgM in control and infected group newborns were $11.38 \pm 6.76$ and $98.7 \pm 58.7$ mg% respectively.
Khatua et al (1984) studied humoral immunity, morbidity and mortality from infective diseases of 50 newborns and reported that cord serum IgM values were significantly raised (≥ 20 mg%) in infants whose mother had infective ailments during pregnancy.

Mehta et al (1987) studied serum IgM levels in 70 septicemic and 40 normal neonates to evaluate its usefulness as a diagnostic and prognostic tool in neonatal septicemia. The workers, reported significantly higher serum IgM levels in cases of septicemia than in their control group of cases.

Complement C₃ -

Johnston et al (1979) expressed their views regarding the role of complement in the host defence mechanism. Though complement plays an integral role in the host defence against infection but with the possible exception of viruses (Mills and Cooper, 1978), complement does not appear to play an important role in resistance to infection by intra-cellular parasites. Whether the newborn infant is actually predisposed to infection because of the complement deficiencies, remains to be proved.

Tandon et al (1984) studied serum C₃ levels in infected newborns and concluded that the low cord serum C₃ levels predispose neonates to increased risk of
infection due to (i) lower opsonic activity as low C₃ levels cause lesser enhancement of IgG and IgM activity, and (ii) deficient chemotactic activity.

Singh (1986) studied thirty two neonates with clinical and bacteriological evidence of infection. Twenty four healthy neonates served as controls for their study. Blood samples were taken for complement estimation. The worker reported that the infected neonates showed breakdown products of complement component C₃ and these breakdown products were detected in 34.4% of infected patients. However, breakdown products of C₃ were not detected in any of the healthy controls. The worker concluded from the above study that complement breakdown products of C₃ can be utilized as a diagnostic tool in case of neonatal infections.

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