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Review article

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A review on comparison of specific serum immunoglobulin g and complement c3 levels in gestational diabetics and normal healthy pregnant women and its complications during pregnancy.

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ABSTRACT

Gestational diabetes mellitus is one of the most common medical complication and a metabolic disorder that occurs during pregnancy. The essential components of humoral immunity are complement and circulating immunoglobulin. Immunoglobulin (Ig), is a large, Y-shaped protein produced mainly by plasma cells that is used by the immune system to identify and neutralize pathogens such as bacteria and viruses. The complement system, a complex protein network initially identified as part of the innate immune system, is as an essential regulator of cell and tissue homeostasis.. Maternal antibodies Ig G are transported across the placenta which protects the newborn. As there are only few studies in Indian literature regarding the comparison of specific serum immunoglobulin g and complement c3 levels in gestational diabetics and normal healthy pregnant women. This review is design to compare the levels of serum immunoglobulin G and complement C3 in Gestational diabetics and normal healthy pregnant woman and its complications during pregnancy.

Keywords- Gestational diabetes mellitus, Immunoglobulin G, Complement C3, Immunity, Complications

INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most common medical complications and a metabolic disorder that occurs during pregnancy. The disease has important health implications for mother and child. Gestational diabetes is a type of diabetes and is defined as impaired glucose

tolerance (IGT) with onset or first recognition during pregnancy. Having diabetes means the amount of sugar in your blood is higher than normal. GDM is a disease of the pancreatic β cells, which do not produce sufficient insulin to meet the increased requirements of late pregnancy [1, 8]. Immunoglobulin (Ig), is a large, Y-shaped protein

produced mainly by plasma cells that is used by the immune system to identify and neutralize pathogens such as bacteria and viruses. The antibody recognizes a unique molecule of the harmful agent, called an antigen, via the Fab's variable region. Each tip of the "Y" of an antibody contains a paratope (analogous to a lock) that is specific for one particular epitope (similarly analogous to a key) on an antigen, allowing these two structures to bind together with precision.

The complement system is an ancient component of the innate immune system; some of its major proteins appeared in echinoderms and exist in each deuterostome. The complement system contains more than 30 proteins in various tissue fluids and on the surface of cells, including proteins of the enzymatic cascade, regulators and receptors. [7] The complement system, a complex protein network initially identified as part of the innate immune system, is as an essential regulator of cell and tissue homeostasis. Complement 3(C3) is the central component of the complement system which induce inflammatory, immunomodulatory and metabolic responses.

The relation between C3 and incidence of diabetes could reflect a systemic low-grade inflammation and the actions of these cytokines. The relation between diabetes and inflammation could also be associated with hepatic production of glucose. The essential components of humoral immunity are complement and circulating immunoglobulin [2]. Maternal antibodies Ig G are transported across the placenta which protects the newborn. This passive immunity acquired by the fetus is crucial for the adaptation of the newborn to the extra uterine environment, providing protection against infections ⁽⁴⁾. Hyperglycemia alters Ig G transfer across the placenta and decreases immunoglobulin levels in maternal blood and colostrum. Maternal diabetes alters the transfer of antibodies through the placenta and colostrums. The reduction in immune reactive protein production may be related to changes in the metabolism of carbohydrates, lipids, and proteins, as well as in various organ systems caused by the hyperglycemic status of pregnant women. [5]

Recent advances in transplantation immunology have stimulated considerable interest in immunologic aspects of pregnancy. Pregnancy maybe considered as a state wherein the foetus exists as a well tolerated homograft. It is possible

that the foetus escapes the process of rejection due to depression of maternal immune responses. Conversely, a disturbance in immunologic tolerance may lead to abortion. [4]

Suppression of maternal immune response may be one of the factors contributing to continuation of pregnancy, a state in which the foetus exists as a well-tolerated homograft. Studies on serum immunoglobulin levels in pregnancy have shown varying results. In some, serum IgG levels showed a graded significant decrease in normal pregnancy compared to the non-pregnant population; IgM levels rose in late pregnancy while IgA increased with pregnancy. In other studies, IgG and IgM declined progressively throughout gestation with a tremendous significant decrease between the first and second trimesters and between the second and third trimesters in pregnant women than those of age-matched non-pregnant control subjects, there was also a significant decrease between the second and third trimester groups. the mean IgG and IgM levels markedly increased in pregnant women, especially Ig G concentration, in the final trimester of pregnancy, which is in association with enhanced Ig G transport through the placenta to the fetus during late pregnancy period [2].

Pregnancy changes affecting disease severity can be attributed to placental or maternal hormones, increased circulation, increased fluid volume, metabolic rate, hemodilution, circulating fetal cells, or other factors. The C3 level was associated with maternal leukopenia, elevated serum C-reactive protein (CRP) elevation, hematuria, hypertension, and preterm premature rupture of membranes. The C4 level was associated with maternal proteinuria, hematuria, hematologic disease, and admission to the neonatal intensive care unit. [3]

REVIEW OF LITERATURE

Deepa K et al;(2015) [1] Conduct a study on 90 pregnant females aged between 20-40yrs, the objectives of the present study was to estimate the serum levels of complement3 (C3) & Immunoglobulin (Ig) G in Gestational Diabetic and to compare the above parameters with normal pregnant females .The study showed significant increase in complement C3 levels and decrease in immunoglobulin G levels in Gestational Diabetes, when compared with normal pregnancy.

Complement 3(C3) is the central component of the complement system which induce inflammatory, immunomodulatory and metabolic responses. This passive immunity acquired by the fetus is crucial for the adaptation of the newborn to the extra uterine environment, providing protection against infections. Complement C3 estimation in GDM could help to understand the underlying chronic inflammation which in turn affects the growing fetus innate immune system and predisposes the individual for future Diabetes and its complications.

Tariah F.S et al ;(2016) [2] conduct a study on 200 female subjects comprising four groups of 50 subjects each were recruited into the study: healthy non-pregnant subjects (Group A); healthy pregnant subjects (Group B); subjects with pre-eclampsia (Group C) and subjects with gestational diabetes mellitus (Group D). The objective of the study to estimate the Serum concentrations of IgA, IgG and IgM were determined in subjects with pre-eclampsia and gestational diabetes as compared to both apparently healthy pregnant and non-pregnant subjects. Significant differences were observed in the values of the various types of immunoglobulins studied between healthy non-pregnant (group A) subjects and healthy pregnant (group B) subjects. Noteworthy is the observation that the values of both IgG and IgM were significantly higher while the values of IgA were significantly lower amongst the non-pregnant subjects in group A, compared to all the other pregnant subject groups: B, C and D. Furthermore, group B subjects were found to have significantly higher values of IgG and lower levels of IgM compared to groups C and D subjects. Values of IgA were significantly higher in all pregnant groups compared to the non-pregnant subjects but highest in the GDM (group D) women.

Dong Kim et al ; (2011) [3] conduct to evaluate the correlation between complement (C3 and C4) levels, anti-dsDNA titers, autoimmune target test (AITT), and pregnancy complications. They evaluated the course of the pregnancy and outcome, pregnancy complications, progression of SLE, maternal complications of SLE, drugs taken before and after pregnancy, neonatal outcomes, and C3/C4 levels, anti-dsDNA titers, and AITT results. The C3 level was associated with maternal leucopenia, elevated serum C-reactive protein (CRP) elevation, hematuria, hypertension, and preterm premature

rupture of membranes. The C4 level was associated with maternal proteinuria, hematuria, hematologic disease, and admission to the neonatal intensive care unit. The anti-ds DNA titer was associated with elevated maternal serum CRP, oligohydramnios, and neonatal anti-Sjögren's syndrome B (La) antibody. The result show that adding the AITT to conventional C3/C4 and anti-ds DNA testing in gravidas with SLE might help antenatal care.

Meena A. et al; (1991) [4] In this study serum immunoglobulin levels of Ig G, Ig A and Ig M were estimated in 75 normal pregnant women, 25 in each trimester. These were compared with a control group of 25 healthy women. Suppression of maternal immune response may be one of the factors contributing to continuation of pregnancy, a state in which the foetus exists as a well tolerated homograft. Studies on serum immunoglobulin levels in pregnancy show varying results. A graded significant decrease in Ig G levels was observed throughout the pregnancy.

Ig A levels decreased during the first and second trimester of pregnancy. A significant increase in Ig M levels from the first to third trimester was observed.

Leslie J. Vaughan (2014) [5] Upon a medicine's approval, the U.S. Food and Drug Administration assigns it one of five pregnancy categories that indicate the potential of a drug to cause harm to the fetus if used during pregnancy. Each category outlines whether clinical studies have shown any potential risks of the drug during pregnancy. IG falls under category C, which means that either no animal or human studies have been conducted or animal reproduction studies have shown drugs in this category to have an adverse effect on the fetus, but there are no well-controlled studies conducted on humans to date. IG's potential benefits may warrant its use despite potential risks. Studies of patients who were receiving IG for a chronic condition prior to becoming pregnant, and continued to receive IG during the course of their pregnancy. And, each of the studies found it was safe to continue IG therapy with no adverse events noted for the mother or the baby. Three of these studies focused on patients with common variable immune deficiency who were treated with IG during pregnancy and whether dose adjustments were needed. The common result from each of these studies found dosing adjustment was

necessary during the course of the pregnancy to keep IgG trough levels at pre-pregnancy levels. The need for increased dosing in the late second and third trimesters is thought to be due to plasma volume expansion. The studies also found that babies born to immune deficient patients who continued IG therapy during pregnancy had adequate IgG levels after birth, whereas babies whose immune-deficient mothers were not treated throughout pregnancy had slightly lower birth weights and presented with lower IgG trough levels.

Malek A et al; (1996) [6] conducted a study by collecting blood samples in between 17-41 weeks of gestation (WG) by puncture of a peripheral maternal vein and by cordocentesis (17-36 WG, n = 91) or directly at delivery (37-41 WG n = 16) from the umbilical vein. Additional maternal samples were collected from the same individual (n = 16) at 10, 20, 30 WG, and at term. The concentration of IgG and its four subclasses and of IgA were determined in the sera using ELISA method. The mean level of IgG and IgA in maternal sera at 9-16 WG was 13.72 +/- 2.53 g/L and 3.95 +/- 1.23 g/L, respectively. Both, IgG and IgA throughout pregnancy decreased to a level of 60-70% (37-41 WG) of the initial concentration in early pregnancy. In the fetal circulation a continuous rise in the level of both IgG and IgA was observed between 17 and 41 WG. Fetal level of IgG at 17-22 WG was only 5-10% of the maternal level and at term exceeded the maternal level reaching a value of 11.98 +/- 2.18 g/L. IgG1 at 17-22 WG was 0.93 +/- 0.42 g/L, which is approximately three times higher than IgG2. IgG1 showed an exponential rise and at 37-41 WG its concentration was seven times higher than IgG2. IgG3 and IgG4 also showed an exponential rise and at term reached a similar level as in the maternal circulation. Striking was the difference in results for IgG2 with a slow linear rise throughout gestation. The fetal IgG2 level at term remained significantly below the maternal concentration. Comparison of fetal and maternal levels of immunoglobulins indicate that the human

placenta during pregnancy develops a specific transport mechanism for IgG.

A.Lubenko et al: (1994) [9] conducted a study of the relationship of hemolytic disease of the newborn (HDN) to the transplacental passage of the four IgG subclasses was assessed at various gestational ages by comparing the maternal and fetal IgG subclass concentrations in 34 pregnancies at risk of HDN with those in 30 pregnancies not at risk. Higher maternal and fetal IgG1 levels were attained in pregnancies at risk of HDN than in pregnancies not at risk. In contrast, a slight decrease in maternal IgG2 and IgG4 levels occurred in pregnancies at risk of HDN, as compared with a slight rise in maternal IgG2 and IgG4 levels in pregnancies not at risk of HDN. Changes in fetal IgG2 and 4 concentrations in either type of pregnancy were very similar, showing only slight increases between the 19th and 34th week of gestation. A slight decrease in maternal IgG3 occurred in both types of pregnancy. In contrast, higher and fairly steady levels of fetal IgG3 were observed in fetuses not at risk of HDN throughout gestation, when compared with those in at risk pregnancies.

CONCLUSION

Gestational diabetes mellitus (GDM) is one of the most common medical complications in pregnancy. The essential components of humoral immunity are complement and circulating immunoglobulin. . Hyperglycemia alters Ig G transfer across the placenta and decreases immunoglobulin levels in maternal blood and colostrums. Complement C3 estimation in GDM could help to understand the underlying chronic inflammation which in turn affects the growing fetus innate immune system and predisposes the individual for future Diabetes and its complications. This review concluded that there is a significant difference in complement C3 levels and immunoglobulin levels in Gestational diabetes, when compared with normal pregnancy.

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