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Study of the Levels of Immunoglobulin G and Complement 3 in Gestational Diabetes and Their Newborn

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ABSTRACT

Background: The most typical metabolic issue related to pregnancy is gestational diabetes. Because it eliminates undesired germs and causes inflammation, the complement system (C3) is an essential part of the cellular immune system. It has been linked to metabolic diseases, including diabetes, obesity, dyslipidemia, insulin resistance, and liver dysfunction. C3 is also becoming more well recognized as a risk factor for cardiovascular and metabolic diseases. Immunoglobulin levels in maternal blood and colostrum are decreased by hyperglycemia, which also affects IgG transfer across the placenta.

Aim of study: to compare the levels of C3 and immunoglobulin G in the sera of pregnant women with gestational diabetes and their babies to pregnant women without the disease.

Methods: a case control study that was carried out over the course of four months, from August 18 to December 20, 2020, at the department of obstetrics and gynecology at Salahaddin General Hospital/Salahaddin. It involved 92 pregnant women who separated into two groups and went to the delivery room to deliver a viable fetus: 47 pregnant women in the case group had been diagnosed with gestational diabetes mellitus, whereas the 45 pregnant women in the control group had no complaints and were matched with the other groups' ages and gestational ages. Results for C3 and IgG levels in maternal and cord blood were noted.

Results: In this study, the case group's mean birthweight and maternal serum C3 levels were both considerably greater than those of the controls. The mean cord serum IgG level in the case group was substantially lower than that in the controls.

Conclusion: Understanding the underlying chronic inflammation that affects the developing fetus' innate immune system and predisposes the person to future diabetes and its consequences may be possible with complement C3 estimate in GDM.

KEYWORDS: Immunoglobulin G, pregnancy, Complement C3, , gestational DM, Iraq.

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1.INTRODUCTION

During pregnancy, women who have never been diagnosed with diabetes acquire persistent hyperglycemia, which is known as gestational diabetes mellitus (GDM), a significant pregnancy complication. The majority of the time, chronic insulin resistance combined with decreased glucose tolerance brought on by dysfunctional pancreatic beta cells results in this hyperglycemia. Although it is possible at any point in the pregnancy, it seems to occur more frequently in the second or third trimester. GDM carries dangers for the mother as well as the fetus. While the mother and infant are alive, some of these hazards still exist(1, 2). The most typical metabolic issue related to pregnancy is GDM. GDM is projected to have impacted 18 million live births globally in 2017 (3). Globally, the prevalence of GDM, which ranges between 1 and 20%, is increasing along with that of obesity and type 2 diabetes mellitus (T2DM). The frequency of T2DM in a particular community or ethnic group directly correlates with the quantity of GDM (4). Because of the updated criteria for GDM screening and diagnosis (5, 6), the prevalence of GDM has recently grown by 2-3 times, ranging from 8.953.4%. The highest incidence of GDM was found in South-East Asia at 24.2%, while the lowest frequency was found in Africa at 10.5%. Nearly 90% of instances of pregnancy-related hyperglycemia took place in low- and middle-income nations, where access to maternal healthcare is scarce. The frequency of GDM differs even within nations based on race/ethnicity and socioeconomic position. The most

vulnerable populations for GDM include those from Aboriginal Australia, the Middle East, and Pacific Islands (7). GDM is characterized by increased insulin resistance during pregnancy, which is brought on by placental hormones such as cortisol, progesterone, human placental lactogen, prolactin, and estradiol, as well as by elements such as leptin, TNF-, and resistin (8, 9, 10), with TNF-levels inversely correlated with changes in insulin sensitivity (11). The HGF/c-MET signaling pathway may be involved in -cell adaptation to meet increased insulin requirements during pregnancy, as deletion of this route is linked to improper adaptation and increased risk of GDM. Although syncytiotrophoblast membrane expression of GLUT3/GLUT4 increases during pregnancy (12), glucose transport across the placenta also plays a role. The precise mechanisms underlying why some women develop GDM despite these typical adaptive changes are still unknown, but they may be related to autoimmunity, genetics, obesity, or other factors (10). Neonatal hypoglycemia and fetal macrosomia can result from untreated GDM (10, 13).

The cause of gestational diabetes mellitus is thought to be a combination of significant insulin resistance brought on by placental hormone release, pancreatic beta-cell malfunction, or a delayed response of the beta cells to glycemic levels (14). The primary hormone associated with increased insulin resistance in GDM is human placental lactogen. Growth hormone, prolactin, corticotropin-releasing hormone, and progesterone are additional hormones linked to the onset of this condition. These hormones help to promote insulin resistance and hyperglycemia during pregnancy (14, 15).

Human serum contains a lot of immunoglobulin G (IgG), which accounts for 10–20% of plasma protein. With IgM, IgD, IgA, and IgE, it makes up the majority of the immunoglobulin subclasses. These glycoproteins' effector activities and heavy chain structures differ. There are four subtypes of IgG: IgG1, IgG2, IgG3, and IgG4. Despite having a great deal in common, each subclass differs in terms of how it binds to antigens, forms immune complexes, activates complement, activates effector cells, maintains a half-life, and transports placenta (16).

Central to the immune system is complement C3, which has been connected to metabolic diseases and identified as a cardio-metabolic risk factor (17). Due to systemic inflammation and hepatic glucose synthesis, its levels are correlated with insulin and glucose (18). Insulin resistance is exacerbated by the production of C3 by adipocytes and inflammatory cells (19). The placenta transmits maternal IgG antibodies to the fetus, which are vital for humoral immunity and offer critical defense against infections (20). This transmission, however, can be hampered by maternal diabetes, which lowers immunoglobulin levels in both maternal blood and colostrum. This is probably because of metabolic modifications brought on by pregnancy-related hyperglycemia (18). According to a 2015 study, gestational diabetes is associated with higher C3 levels and lower IgG levels in neonates compared to gestational diabetes-free pregnancies (18). However, there is little reliable information on C3 and IgG levels in gestational diabetes. In order to better understand gestational diabetes and its effects on neonates, this study will look at C3 and IgG levels.

The Aim of this study is To compare levels of C3 and immunoglobulin G in the sera of gestational diabetic mothers and their newborns with non-diabetic mothers and their newborns.

MATERIL AND METHODS

2. 1Study design, setting and data collection time

This case control study was carried out over the course of four months, from August 18 to December 20, 2020, at the Department of Obstetrics and Gynecology at Salahaddin General Hospital.

2. 2Study patients and sample size

In the beginning, 96 pregnant women participated in the research and went to the delivery room to deliver a viable fetus. They were made aware of the purpose of the study, and their verbal agreement was acquired. Data were gathered using a questionnaire created specifically for the study. The total number of women included in the study was 92 since four individuals had invalid or missing C3 or Igg values. Two groups of the study's involved women were created.

• **Case group**: Included 47 pregnant women who had diagnosed with gestational DM.

• **Control group**: Includes 45 pregnant women without any complaint matched with the other groups in age and gestational age.

Earlier in the pregnancy, prenatal care visits confirmed the diagnosis of gestational diabetes mellitus (DM). The first day of the last menstrual cycle was used to determine gestational age at the time of presentation, and an early abdominal ultrasound examination was used to confirm it.

Exclusion criteria

• Overt DM

2.3. Sample collection and C_3 and IgG test procedures

All pregnant women had a four-ml blood sample taken from the volar surface of their forearms at presentation, and a second four-ml sample was taken from the umbilical cord during childbirth to test for C3 and IgG levels. Enzyme-linked immunosorbent assay based on biotin double antibody sandwich technique was used to test IgG and C3 kit principles.

2.4. Ethical considerations and official approvals

Prior to gathering data, each patient gave their verbal consent, and the information was anonymized. Names were deleted, and identifying numbers were used instead. Every piece of information is kept private on a laptop with a password, and the data is only utilized for study.

2.5. Statistical analysis

Version 25 of the Statistical Package for Social Sciences (SPSS) was used to analyze the data. The data were provided as mean, SD, and ranges. expressed as frequencies and percentages for categorical data. Accordingly, the continuous variables were compared using an independent t-test (two tailed). The connection between maternal and cord C3 and IgG levels and certain continuous variables was evaluated using Pearson's correlation test (r). P values of less than 0.05 were regarded as significant levels.

3.0 RESULTS

3.1. Demographic Data

The distribution of study groups by demographic data is shown in table (3.1 and 3.2). Study patient's age was ranging from 16 to 40 years with a mean of 29.9 years and standard deviation (SD) of ± 6.57 years. The highest proportion of study patients case and control groups was aged between 21 – 35 years (57.4% and 46.7% respectively). Regarding BMI level, the highest proportion of patients in case group was obese (44.2%). While 64.4% of controls were overweighed).

About gravidity, we noticed that the highest proportion of patients in case and control groups were ≥ 3 (66% and 57.8% respectively).

We noticed that women in case and control groups were finished primary school (42.6% and 55.6% respectively); presented with term pregnancy (66% and 80% respectively); delivered by NVD (59.6% and 77.8% respectively)

The majority of those who underwent C/S in case and control groups were delivered by general anesthesia (78.9% and 70% respectively)

There were no statistically significant differences (P ≥ 0.05) between the study groups in age, BMI level, and parity.

Table 3.1: Distribution of the study patients' groups by general characteristics

General Characteristics	Study Groups		Total (%) n= 92
	Case (%) n= 47	Control (%) n= 45	
Age (Year)			
< 25	6 (12.8)	8 (17.8)	14 (15.2)
25 – 34	27 (57.4)	21 (46.7)	48 (52.2)
≥ 35	14 (29.8)	16 (35.6)	30 (32.6)
BMI Level			
Normal	12 (27.9)	16 (35.6)	28 (31.8)
Overweight	12 (27.9)	29 (64.4)	41 (46.6)
Obese	19 (44.2)	0 (0)	19 (21.6)
Gravidity			
< 3	16 (34.0)	19 (42.2)	35 (38.0)
≥ 3	31 (66.0)	26 (57.8)	57 (62.0)
Educational level			
Illiterate	7 (14.9)	16 (35.6)	23 (25.1)
Primary school	20 (42.6)	25 (55.6)	45 (48.9)
Secondary school	8 (17.8)	4 (8.9)	12 (13.0)
Higher education	12 (25.5)	0 (0)	12 (13.0)
Socioeconomic status			
BPL	0 (0)	12 (26.7)	12 (13.0)
APL	47 (100.0)	33 (73.3)	80 (87.0)
GA			
Preterm	16 (34.0)	9 (20.0)	25 (27.2)
Term	31 (66.0)	36 (80.0)	67 (72.8)
Mode of delivery			
NVD	28 (59.6)	35 (77.8)	63 (68.5)
C/S	19 (40.4)	10 (22.2)	29 (31.5)
Type of anesthesia	**n= 19**	**n= 10**	**n= 29**
General Anesthesia	15 (78.9)	7 (70.0)	22 (75.9)
Spinal	4 (21.1)	3 (30.0)	7 (24.1)

The comparison between study groups by certain characteristics is shown in table (3.2). Mean of BMI was significantly higher in patients of case group than that in controls (29.37 versus 25.85 kg/m2, P= 0.001).

There were no statistically significant differences (P ≥ 0.05) between the study groups in age, BMI, GA, and gravida.

Table 3.2: Comparison between study groups by certain characteristics

Variable	Study groups		P - Value
	Case Mean ± SD	Control Mean ± SD	
Age (Years)	30.12 ± 5.4	29.91 ± 7.9	**0.879**
BMI (kg/m^2)	29.37 ± 5.7	25.85 ± 1.7	**0.001**
Gravida	3.0 ± 1.3	3.11 ± 2.4	**0.784**
GA (Week)	37.7 ± 2.4	38.17 ± 2.6	**0.363**

3.2. Laboratory Investigation

The comparison in means of laboratory investigation between study groups is shown in table (3.3). We noticed that, means of RBS, HbA1c, SGOT, TSB, blood urea, and s. creatinine were significantly higher (P= 0.001) in patients with GDM compared to that in women in the control group.

Mean of platelet count was significantly lower (P= 0.001) in women with GDM compared to that in normal pregnant women.

There were no significant differences in means of Hb, WBC count, and SGPT (P ≥ 0.05) between study groups.

Table 3.3: Comparison in laboratory investigation between the study groups

Lab. Investigation	Study group		P - Value
	Case Mean ± SD	Control Mean ± SD	
RBS (mg/dl)	128.55 ± 52.9	85.28 ± 30.5	**0.001**
HbA1c (%)	6.28 ± 0.94	4.5 ± 0.37	**0.001**
Hb (gm/dl)	11.79 ± 1.0	11.43 ± 1.1	**0.12**
WBC (10 ^{9}/l)	10.97 ± 2.1	11.3 ± 1.5	**0.389**
SGOT (U/l)	25.96 ± 6.1	21.24 ± 4.0	**0.001**
SGPT (U/l)	23.99 ± 7.7	22.6 ± 3.7	**0.297**
TSB (mg/dl)	0.83 ± 0.4	0.64 ± 0.13	**0.005**
Urea (mg/dl)	31.65 ± 6.7	25.26 ± 4.7	**0.001**
Creatinine (mg/dl)	0.76 ± 0.07	0.62 ± 0.07	**0.009**
PLT Count (10 ^{9}/l)	241.0 ± 48.4	310.42 ± 83.2	**0.001**

3.3. Pregnancy outcome

Table 3.4 shows the comparison in birthweight and Apgar score between study groups. Mean of BW was significantly higher in case group than that in controls (3.75 versus 2.96 kg, P= 0.001).

No statistical significant difference detected in Apgar score (P= 0.113) between study groups.

Table 3.4: Comparison between study groups by birthweight and Apgar score

Pregnancy outcome	Study groups		P - Value
	Case Mean ± SD	Control Mean ± SD	
Birthweight (kg)	3.75 ± 0.77	2.96 ± 0.52	**0.001**
Apgar score at 5th mint.	7.02 ± 1.4	7.64 ± 2.2	**0.113**

3.4. Complications of newborn

The distribution of study groups by newborn complication is shown in table (3.5). In this study, 83% of newborns of case group and 82.2% of those of controls were developed hyperbilirubinemia.

Regarding hypoglycemia, it was presented mostly in case group (91.5%) as compared to
8.9% in controls.

Seizure was noticed in 42.6% of case group and 17.8% of controls.

Table 3.5: Distribution of study groups by newborn complication

Newborn complication	Study Groups		Total (%) n= 92
	Case (%) n= 47	Control (%) n= 45	
Hyperbilirubinemia			
Yes	39 (83.0)	37 (82.2)	76 (82.6)
No	8 (17.0)	8 (17.8)	16 (17.4)
Hypoglycemia			
Yes	43 (91.5)	4 (8.9)	47 (51.1)
No	4 (8.5)	41 (91.1)	45 (48.9)
Seizure			
Yes	20 (42.6)	8 (17.8)	28 (30.4)
No	27 (57.4)	37 (82.2)	64 (69.6)

3.5. Complement C_3 level

Table 3.6 and figure 3.1 show the comparison in maternal and cord C3 levels between study groups. Mean of maternal serum C3 level was significantly higher in case group than that in controls (811.14 versus 588.0 µg/ml, P= 0.001).

No statistical significant difference detected in cord serum C3 level (P= 0.066) between study groups.

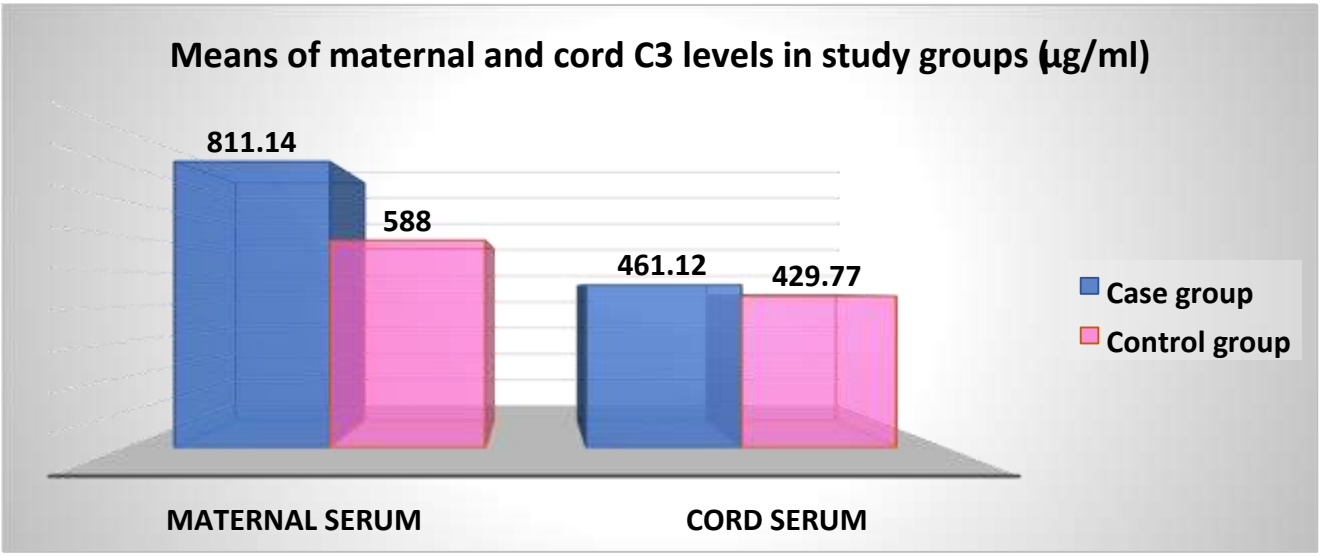

Figure 3.1: Means of maternal and cord C3 levels in study groups

Table 3.6: Comparison between study groups by maternal and cord C3 levels

Complement C3 levels (µg/ml)	Study groups		P - Value
	Case Mean ± SD	Control Mean ± SD	
Maternal serum	811.14 ± 114.8	588.0 ± 170.1	**0.001**
Cord serum	461.12 ± 75.8	429.77 ± 85.3	**0.066**

3.6. Immunoglobulin G level

Table 3.7 and figure 3.2 show the comparison in maternal and cord IgG levels between study groups. Mean of cord serum IgG level was significantly lower in case group than that in controls (17.06 versus 24.89 µg/ml, P= 0.001).

No statistical significant difference detected in maternal serum IgG level (P= 0.84) between study groups.

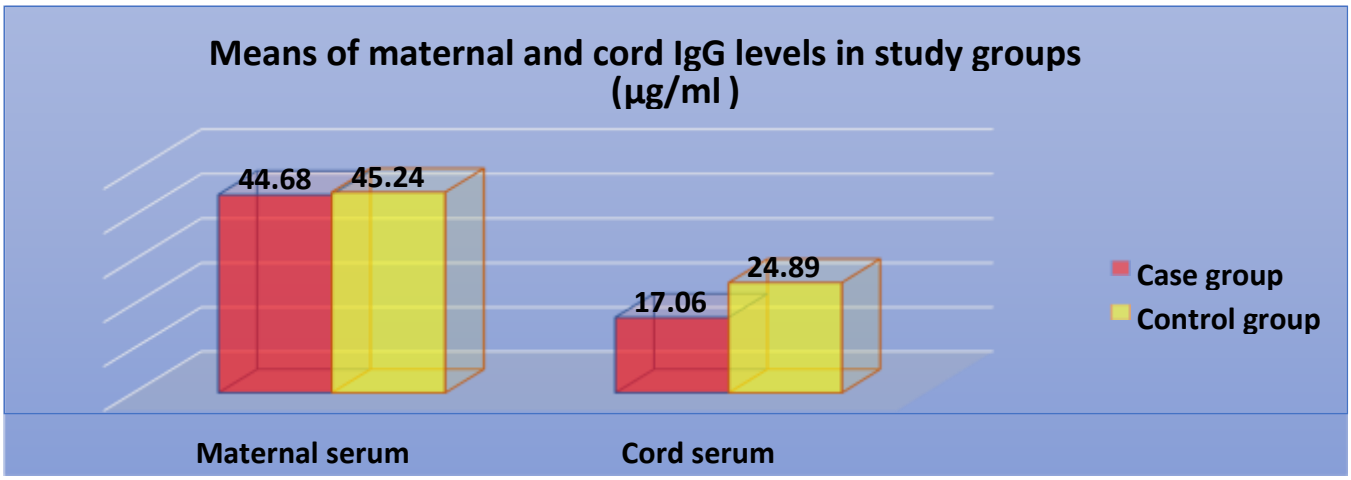

Figure 3.2: Means of maternal and cord IgG levels in study groups

Table 3.7: Comparison between study groups by maternal and cord IgG levels

Immunoglobulin G levels (µg/ml)	Study groups		P - Value
	Case Mean ± SD	Control Mean ± SD	
Maternal serum	44.68 ± 15.4	45.24 ± 10.5	**0.84**
Cord serum	17.06 ± 5.7	24.89 ± 9.6	**0.001**

3.7. Correlation between maternal and cord C_3 with certain parameters

Statistically significant weak positive correlations were detected between maternal C_3 level and RBS (r= 0.327, P= 0.001), and birthweight (r= 0.383, P= 0.001). Statistical significant moderate positive correlation was detected between maternal C_3 level and HbA1c (r= 0.473, P= 0.001). Statistical significant weak negative correlation was detected between maternal C_3 level and WBC (r= - 0.279, P= 0.008)

Regarding cord C_3 level, there were significant weak positive correlations with RBS (r= 0.385, P= 0.001), TSB (r= 0.262, P= 0.016), and BW (r= 0.283, P= 0.006).

No statistical significant correlations between maternal or cord C_3 levels with all other parameters as shown in table (3.8)

Table 3.8: Correlation between maternal and cord C_3 with certain parameters

Variable	Maternal C_3 (µg/ml)		Cord C_3 (µg/ml)	
	r	P - Value	r	P - Value
RBS (mg/dl)	**0.327**	**0.001**	**0.385**	**0.001**
HbA1c (%)	**0.473**	**0.001**	**0.037**	**0.731**
WBC (10^9/l)	**- 0.279**	**0.008**	**0.06**	**0.581**
SGOT (U/l)	**0.211**	**0.121**	**0.174**	**0.114**
SGPT (U/l)	**0.045**	**0.682**	**0.179**	**0.104**
TSB (mg/dl)	**0.215**	**0.064**	**0.262**	**0.016**
Birthweight (kg)	**0.383**	**0.001**	**0.283**	**0.006**

3.8. Correlation between maternal and cord IgG with certain parameters

Statistically significant weak negative correlations were detected between maternal IgG level and RBS (r= - 0. 27, P= 0.001), HbA1c (r= - 0.265, P= 0.013), WBC (r= - 0.365, P= 0.001), and birthweight (r= - 0.336, P= 0.001).

Regarding cord IgG level, there was significant moderate negative correlation with HbA1c (r= - 0.54, P= 0.001) and weak negative correlation with RBS (r= - 0.232, P= 0.026).

No statistical significant correlations between maternal or cord IgG levels with all other parameters as shown in table (3.9)

Table 3.9: Correlation between maternal and cord IgG with certain parameters

Variable	Maternal IgG (µg/ml)		Cord IgG (µg/ml)	
	r	P - Value	r	P - Value
RBS (mg/dl)	- 0.27	0.009	- 0.232	0.026
HbA1c (%)	- 0.265	0.013	- 0.54	0.001
WBC (10^9/l)	- 0.365	0.001	0.103	0.339
SGOT (U/l)	- 0.116	0.292	0.017	0.877
SGPT (U/l)	- 0.037	0.738	- 0.099	0.368
TSB (mg/dl)	0.123	0.264	0.133	0.562
Birthweight (kg)	- 0.336	0.001	0.053	0.615

4. DISCUSSION

4.1 Overview

Macrosomia, hypoglycemia, hyperbilirubinemia, and respiratory distress syndrome are just a few of the complications that can affect both the mother and the fetus as a result of varying degrees of carbohydrate intolerance (21), which may be brought on by decreased insulin sensitivity or impaired -cell function (22,23). Gestational diabetes mellitus (GDM) typically develops during the second half of pregnancy. Additionally, maternal hyperglycemia can impair the transfer of IgG antibodies across the placenta, reducing the immunity of the unborn child (20). Elevated complement C3 levels are also linked to metabolic diseases like adiposity, dyslipidemia, insulin resistance, and diabetes (7).

4.2 Complement C3 level

In contrast to the control group, women with gestational diabetes mellitus had maternal complement C3 levels that were considerably greater than those in the cord blood (24, 25). These levels also positively correlated with indicators of hyperglycemia and birth weight. This implies immunological dysregulation, which is reflected in higher C3 levels, may influence insulin resistance and beta-cell function, thereby exposing mothers and babies to future diabetes and complications, contributing to the pathophysiology of GDM and subsequent diabetes risk (26,27).

4.3 Immunoglobulin G level

According to the study, neonates of women with gestational diabetes (GDM) had cord blood IgG levels that were considerably lower than those of newborns of moms without GDM. In contrast to cord IgG levels, maternal IgG levels were inversely linked with indices of hyperglycemia, white blood cell count, and birth weight. This is consistent with research from Deepa et al. from 2015 that found reduced IgG levels in babies of GDM moms and reported comparable findings. However, there was no discernible difference in maternal IgG levels between the two groups. IgG levels were lower in diabetes women and their babies, according to a previous study by Fischer and colleagues, but it was also reported that the immune defense mechanisms involving IgG delivery to the fetus were nonetheless equivalent to those of normal pregnancies. The decrease in cord blood IgG might be attributed to immune complex formation or reduced IgG synthesis, highlighting the need of maternal IgG transfer to protect babies, especially when their own immune systems are still developing (27,28).

4.4. Complications of newborn

The risk of problems including hyperbilirubinemia and hypoglycemia in newborns of women with gestational diabetes mellitus (GDM) is increased. In this study, the majority of babies in both the case and control groups had hyperbilirubinemia, whereas the case group's prevalence of hypoglycemia was higher (91.5%) than that of controls (8.9%). Additionally, the case group (42.6%) experienced seizures more frequently than the control group (17.8%). These results are in line with a prior research by Mitrovi et al. from 2014, which indicated that patients with GDM had considerably greater rates of hypoglycemia and hyperbilirubinemia than those without the disease. Other research, including that conducted in 2015 by Wielandt et al, revealed decreased incidence of newborn hypoglycemia. The variations seen in these studies may be caused by elements including gestational age, the type of diabetes in the mother, and problems in the mother. Due to the impact of maternal hyperglycemia on fetal pancreatic cells, decreased gluconeogenesis, altered hormone synthesis, and higher risk of hypoglycemia, neonatal hypoglycemia is seen in children whose mothers have diabetes. (29) (30) (31).

4.5. Pregnancy outcome

Although some studies revealed no changes in Apgar ratings between the groups, others observed greater birth weights in babies of women with gestational diabetes mellitus (GDM) compared to those without GDM or reduced glucose tolerance. To be more precise, one research discovered considerably greater birth weights in the GDM group (3.75 vs 2.96 kg, p=0.001) , while another discovered slightly higher gestational age and birth weight in children of diabetes women. However, one study revealed that the GDM group had lower 1 and 5-minute Apgar scores and higher newborn morbidity . The greater prenatal glucose exposure from GDM was probably the cause of the larger birth weights (32, 33, 34).

4.6 Laboratory Investigation

In the present work, means of RBS, HbA1c, SGOT, TSB, blood urea, and s. creatinine were significantly higher in

patients with GDM compared to the control group, while platelet count was lower (P=0.001). One study similarly found HbA1c and FBG to be significantly increased in GDM patients at the third trimester stage compared to controls (8.64 ± 0.72 vs 5.34 ± 0.39 for HbA1c; 198.08 ± 33.12 vs 96.36 ± 6.63 for FBG) (35). However, another study found fasting glucose levels between GDM and control groups to be only marginally different (p=0.0217) and HbA1c values between GDM patients and controls not to differ meaningfully based on GDM management type (36). Elevated third trimester FBG and HbA1c levels in GDM agree with their role as indicators for diagnosing GDM and predicting adverse pregnancy outcomes (37, 38). Differences between studies may relate to factors like sample size, pathophysiology, infections, and gestation course.

4.7. Demographic Data

In the present study, the mean age was 29.9 ± 6.57 years ranging from 16-40 years, and 44.2% of cases were obese while 64.4% of controls were overweight. This is consistent with other studies that found higher BMI in GDM groups compared to controls (36). One study found a mean age of 30.48+5.83 years and mean BMI of 24.80+3.15 kg/m2, with early GDM group having significantly higher BMI . Another study found most common age was 20-29 years, 60% had BMI ≥30 kg/m2, and 60% were primigravidas (39). A separate study found no significant difference in mean age between GDM and control groups (28.28 ± 6.40 years), while another reported a mean age of 33.3±5.6 years and mean BMI of 32.0±5.5 kg/m2, with 75% being housewives and 60% having a family history of diabetes (40, 41). Thus several studies consistently reported higher BMI in GDM groups.

5. CONCLUSION

Complement C3 estimation in GDM may be able to shed light on the chronic inflammation that underlies the condition and affects the developing fetus' innate immune system, predisposing the person to future diabetes and its complications.

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