

TOTAL SIALIC ACID AND OTHER INFLAMMATORY MARKERS AS PREDICTORS OF GESTATIONAL DIABETES

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ABSTRACT

Background: Total sialic acid determination has been shown as an inflammatory marker for type 2 diabetes. No local study has been done to characterize the levels of TSA in gestational diabetes.

Objectives: To determine inflammatory markers predictive of gestational diabetes; to be able to describe the clinical profile of subjects enrolled in this study and determine the odds ratio for each inflammatory marker.

Study Design and Methodology: Sixty two pregnant patients in their first trimester were included in this study. Inflammatory markers were measured at 12 weeks and repeated at 24 -28 weeks AOG together with screening glucose tests include random blood sugar at 12 weeks and 75-gram oral glucose tolerance test at 24 -28 weeks. Factors independently associated with impaired glucose tolerance (IGT) and gestational diabetes mellitus (GDM) were determined using logistic regression stepwise model technique.

Results: Of the 62 pregnant patients in their first trimester enrolled in study, five were diagnosed to have GDM based on the American Diabetes Association criteria (ADA), four with IGT and 53 with normal glucose tolerance. At 12 weeks gestation, total sialic acid (TSA) was higher among those with IGT and GDM compared to those with normal glucose tolerance (NGT) (mean=241.5 vs 175 vs 161, $p=.030$). However it was higher in GDM than those with IGT and NGT at 24-28 weeks (mean= 244.8 vs 229.7 vs 177, $p=.025$). Deranged total sialic acid performed at 24-28 weeks showed a trend for association with gestational diabetes (RR=3.6, 95%CI 0-4.53, $p=0.96$). Other factors correlated, include a higher mean age (> 26) and a family history of diabetes mellitus. Factors associated with impaired glucose tolerance, include a deranged TSA at 12 weeks, deranged CRP at 24-28 weeks, a deranged ESR both at 12 and 24-28 weeks gestation and a family history of diabetes mellitus.

Conclusion: Deranged levels of TSA at 24-28 weeks AOG seem to be associated with gestational diabetes.

TSA determination at this gestational age can be utilized to screen gestational diabetes.

Keywords: total sialic acid, gestational diabetes, inflammatory markers

INTRODUCTION

Pregnancy is an immunosuppressive state, even though pregnant women are not notably susceptible to overwhelming infection. Large numbers of leucocytes are present at the maternal-fetal interface, where the detection of multiple cytokines is suggestive of leukocyte activation; granulocytes and monocytes are increased in number in the maternal circulation.¹

There are two arms of the immune system: the innate (non-specific) and adaptive (specific) systems, both of which have cellular and humoral components. The innate system triggers an immune response by processing and presenting antigen in association with major histocompatibility complex, in effect, it instructs the adaptive system to either respond or not. Signals produced by innate receptors cause effector responses to neutralize the stressors and restore homeostasis. The acute phase response is probably the best-studied part of the immune system. These positive acute-phase reactants include fibrinogen, haptoglobulin, C-reactive protein and serum amyloid A. The serum or plasma sialic acid concentration is a marker of the acute phase response.^{1,2,3}

Gestational diabetes mellitus (GDM), defined as glucose intolerance that has its onset or first recognition during pregnancy, occurs in 3-5% of pregnancies. The Asean Federation of Endocrine Societies Study Group on Diabetes in Pregnancy (ASGODIP) reports a prevalence of 14.5%. The Makati Medical Center study showed the prevalence of Gestational Diabetes among Asian population to be 13.4%. GDM and type 2 Diabetes Mellitus have been said to be part of the disease process, although they generally occur at different points during the life span. The importance of the recognition of GDM stems from fetal morbidity and its importance as an independent predictor of type 2 diabetes mellitus.⁴ This was exemplified by high conversion rates from

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previously diagnosed GDM to full blown diabetes from 6.8 to 92% for combined, combined impaired glucose tolerance and overt diabetes and 2.9 to 50% for diabetes alone in a study by Bevier *et al.*⁵ Buchanan and Catalano reported a conversion rate of 6 to 62% (or a cumulative risks of 5-10% per year) for the development of diabetes.⁶ In a study by Wolf *et al*, after delivery of women with Gestational Diabetes has a significant risk of developing type 2 diabetes mellitus and more likely display the features of insulin resistance syndrome which are linked to cardiovascular disease.^{7,8}

Sialic acid is a strong predictor of onset of diabetes even before weight gain or abnormal sugar levels occur. This is a promising new field of research in identifying diabetes-prone patients early, potentially averting complications. A study by Sriharan *et al* in 2002 showed an increased total sialic acid levels are associated with previous GDM.⁹

Increased inflammation during pregnancy as demonstrated by an increase in leukocyte count is associated with the development of GDM. In a study of Wolf *et al* in 2004, there is a linear trend between the increasing leukocyte count and worsening of glucose intolerance. The results were independent of other risk factors for GDM, thus suggesting a dose-response relationship between inflammation and glucose tolerance.⁷

C-reactive protein was positively associated with GDM risk as reported by Qui *et al* in 2004. Inflammation, marked by an increase in C reactive protein level is an independent risk factor for cardiovascular disease. It is also associated with insulin resistance and an independent factor for the development of type 2 diabetes mellitus. A study by Wolf *et al* showed an association between first-trimester inflammation, marked by increase CRP levels, and subsequent risk of GDM. An increase in white cell count, IL-6 and CRP levels were independently associated with increased risk of developing type 2 diabetes.¹⁰⁻¹³

The association of the different inflammatory markers with the onset of Gestational Diabetes will give us a new paradigm for the early detection of GDM and to prevent the development of overt diabetes in postpartum women.

Objectives

General Objective

To determine the inflammatory markers predictive of Gestational Diabetes

Specific Objectives

1. To describe the clinical profile of subjects enrolled in this study.
2. To determine the odds ratio for each inflammatory marker

MATERIALS AND METHODS

All pregnant women seen at the MMC Out patient Department during their first trimester will be recruited from January 1, 2005 to December 31, 2007. Informed consent will be obtained. A random blood glucose (RBG) will be done. Those with RBG ≥ 200 mg/dl (11.1 mmol/L) will be excluded. Those qualified will complete a standard interview (Table I: Questionnaire). The following will be noted: age, parity, blood pressure, BMI, history of GDM, smoking, family history of diabetes. Tests including white blood cell count, CRP and Sialic acid will be done during their first trimester and 24-28 weeks. White blood cell will be measured using the Coulter machine by Beckman and Dickenson. Ultrasensitive C reactive protein (CRP) will be measured using the quantitative method. Serum Sialic acid will be measured using an enzymatic method manufactured by Roche. Patients with known type 1 and type 2 Diabetes Mellitus and those with known diseases like rheumatologic, hypertension or renal diseases or current infections like UTI, Pulmonary disease, will be excluded. On the 24th to 28th week of gestation a 50 gram Oral Glucose Challenge Test (OGCT) will be done on all subjects. Those with (+) OGCT defined as plasma glucose ≥ 130 mg/dl, will undergo a 100 gm Oral Glucose tolerance test (OGTT). GDM is diagnosed by 100 gm OGTT: Fasting Plasma Glucose is >95 mg/dl, one hour plasma glucose >180 mg/dl, 2 hours plasma glucose of >155 mg/dl and 3 hours plasma glucose <140 mg/dl. All those who will be positive for GDM will be noted and treated accordingly.

Table 1: Questionnaire – Initial and Subsequent Visits

Name: Age:
Address:
Phone number:
Phone number of nearest kin:
Date of first visit:
Expected date of confinement:
Obstetrical history: G_P_
Smoking history:
History of GDM: Yes___ No___. If yes, state treatment done and work ups done after delivery _____

(continue next page)

(Table I continuation . . .)

Date			
AOG			
BP			
Weight			
BMI			
wbc			
CRP			
Sialic acid			
OGCT			
OGTT			
Fasting			
1 hr			
2 hr			
3 hr			

Statistical Analysis

Descriptive statistics will compute for measures of central tendency (mean + SD). All inflammatory markers will be converted into a dichotomous category and entered into a stepwise binary logistics regression model to arrive at a best fitted model to predict the occurrence of the dependent variable. The best fitted model will be able to predict the occurrence of the dependent variable at least 50% of the time. All significant odds ratio will be calculated with statistical level of significance of 0.05 and CI.

RESULTS

A total of 62 pregnancies were observed and screened for gestational diabetes mellitus. Five women were confirmed to have GDM, while four had impaired glucose tolerance while 53 had normal glucose tolerance tests. The mean age was 26 years old (range 17-36), with majority (68%) having normal body mass index prior to present pregnancy. One subject had family history of hypertension while seven subjects (12%) have a history of diabetes mellitus.

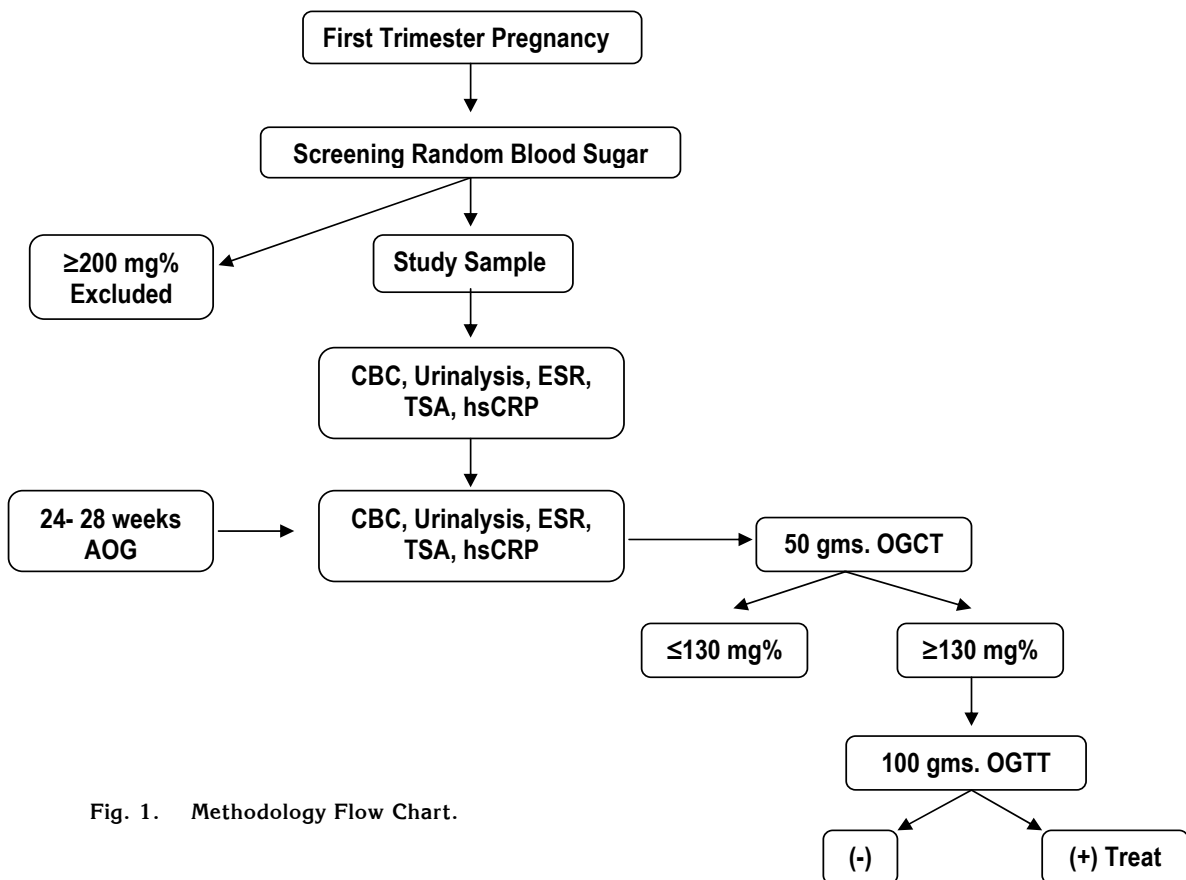


Fig. 1. Methodology Flow Chart.

Table I. Clinical Profile of Pregnancies Tested for Total Sialic Acid and Other Inflammatory Markers, Makati Medical Center, 2008

Characteristic	Frequency (n=62)	Percentage (%)
Age (Years)		
Mean ± SD	26 ± 5	-
Range	17 - 36	
Family History		
Hypertension	1	2
Diabetes mellitus	7	12
Pre-pregnant BMI		
< 18.5	15	24
18.5-24.9	42	68
25-29.9	3	5
≥ 30	2	3
Classification		
Impaired Glucose tolerance	4	6
Gestational Diabetes	5	8
Normal Glucose Tolerance	53	86

Comparison of Inflammatory Markers

Mean white blood cell count was significantly different at 12 weeks. Counts were higher among those with impaired glucose tolerance (IGT) [mean=13,727 vs 10,000 vs 10,017, p=.033]. Values did not significantly vary at 24-28 weeks.

C-reactive protein (CRP) was higher among those with GDM when compared to those with IGT and normal glucose tolerance both at 12 weeks and at 24- 28 weeks. [At 12 weeks 3.4 vs 6.2 vs 0.96, p=.23: at 24-28 weeks 5.5 vs 0.83 vs 1.2, p=.05]

Erythrocyte sedimentation rate was significantly higher among those with GDM at 24-28 weeks when compared to those with IGT and normal glucose tolerance. (Mean 41.6 vs 36 vs 31.3, p=.036).

At 12 weeks of pregnancy, total sialic acid was statistically higher among those IGT than those with GDM and normal glucose tolerance (241.5 vs 175.9 vs 161, p=.030). However at 24-28 weeks values among those with GDM were significantly higher than those with IGT and those with normal glucose tolerance (244.8 vs 229.7 vs 177, p=.025).

Table II. Comparison of Total Sialic Acid and Inflammatory Markers Among 62 Pregnancies, MMC, 2008

Marker (Mean ± SD)	Impaired Glucose Tolerance n=4	Gestational Diabetes n=5	Normal Glucose Tolerance n=53	p-value*
White Blood Cell				
12 Weeks	13,727 ± 2,249	10,000 ± 1,630	10,017 ± 378	.033
24-28 Weeks	12,907 ± 2,795	28,056 ± 16,749	10,567 ± 288	.15
C-reactive Protein				
12 Weeks	0.62 ± .88	3.4 ± 1.6	0.96 ± 1.6	.23
24-28 Weeks	0.83 ± 1.6	5.5 ± 1.8.	1.2 ± 1.7	.05
ESR (mm/hr)				
12 Weeks	31.2 ± 9.4	28.6 ± 5.1	29.8 ± 7.0	.37
24-28 Weeks	36 ± 9.3	41.6 ± 3.2	31.3 ± 3.5	.036
Total Sialic Acid				
12 Weeks	241.5 ± 24.5	175.9 ± 25.4	161 ± 6.4	.030
24-28 Weeks	229.7 ± 16.4	244.8 ± 37.8	177 ± 6.7	.025

*Significant difference if p-value is <.05, Kruskal Wallis ANOVA
 ESR-erythrocyte sedimentation rate (Reference range- < 50 years old Female- 0 to 20mm/hr Male : 0 to 15 mm/hr)
 TSA- Reference range- males = 68.47 ± 4.85 mg % females = 67.77 ± 7.87mg%
 CRP- Reference range- <1.0 mg/ml

Factors Associated with Gestational Diabetes Mellitus and Impaired Glucose Tolerance

Among all variables analyzed, deranged total sialic acid performed at 24-48 weeks showed a trend for association with GDM (RR=3.6, 95% CI 0-4.53, p=.96). Other factors showing trend for association was a higher mean age (RR=2.2, 95% CI 0.1-9.99, p=.99); an abnormal ESR at 12 weeks was 8.9 times associated (95% CI .05-12.2, p=.11); presence of family history of diabetes (RR=6.6, 95% CI .43-33.3, p=.32) (Table III)

Total sialic acid done at 12 weeks, CRP and white blood cell counts in either gestational periods and pre-gestation body mass index were not statistically associated.

Table III. Regression Analysis of Factors Associated with Development of Gestational Diabetes Mellitus, MMC, 2008

Variable	Relative Risk	95% CI	p-value*	Comment
Age	2.2	0.1- 9.999	.99	Trend
TSA at 12 wks	.043	0 -3.25	.98	NS
TSA at 24-28 wks	3.6	0 - 4.53	.96	Trend
CRP at 12 wks	.074	0.03 - 3.44	.78	NS
CRP at 24-28 wks	.01	.006 - 2.2	.08	NS
ESR at 12 wks	8.9	.05 - 12.2	.11	Trend
ESR at 24-28 wks	1.1	0.98 - 4.4	.67	NS
WBC at 12 wks	1.2	0.77 - 3.3	.68	NS
WBC at 24-28 wks	0.8	0.32 - 4.4	.87	NS
Diabetes in Family	6.6	.43 - 33.3	.32	Trend
Hypertension in Family	1.1	.33 - 7.4	.08	NS
Pre-gestation BMI	0.6	.22 - 3.3	.77	NS

*Significant association if RR is > 1, and p-value is <.05, Cox regression, forward technique

Impaired Glucose Tolerance

For impaired glucose tolerance, a deranged TSA at 12 weeks was 3.5 times associated (95% CI 1.1-4.58, $p=.98$); while deranged CRP at 24-48 weeks was almost nine times associated (RR=8.8, 95% CI .23-13.4, $p=.58$), and deranged ESR at 12 and 24-28 weeks were also associated (RR=8.9, 95% CI .05-12.2, $p=.11$) and (RR=251, 95% I 0.88-44.4, $p=.37$). Also, a family history diabetes was associated 4.6 (95% CI .53-13.3, $p=.08$). (Table IV)

Table IV. Regression Analysis of Factors Associated with Impaired Glucose Tolerance, MMC, 2008

Variable	Relative Risk	95% CI	p-value*	Comment
Age	1.2	0.87- 3.3	.89	NS
TSA at 12 wks	.043	0 -3.25	.98	NS
TSA at 24-28 wks	3.5	1.1 - 4.58	.66	Trend
CRP at 12 wks	1.2	0.3 - 13.4	.52	NS
CRP at 24-28 wks	8.8	2.3 - 13.4	.58	Trend
ESR at 12 wks	8.9	.05 - 12.2	.11	Trend
ESR at 24-28 wks	25.1	0.88 - 44.4	.37	Trend
WBC at 12 wks	1.2	0.77 - 3.3	.68	NS
WBC at 24-28 wks	1.5	0.32 - 14.4	.67	NS
Diabetes in Family	4.6	.53 - 13.3	.22	Trend

DISCUSSION

In this prospective study of pregnant women, deranged total sialic acid performed at 24-28 weeks showed a great association with gestational diabetes. Other factors showing trend for association was a higher mean age and values of C- reactive protein noted to be elevated at all age of gestation and higher in women with gestational diabetes. Mean white cell count was significantly different at 12 weeks and did not significantly vary at the latter stage of gestation. Erythrocyte sedimentation rate was significantly high with those with GDM.

In the last few years many scientists have discovered the abnormally high levels of sialic acid in the human serum many pathologic states such as tissue destruction, tissue proliferation, depolymmerization and inflammation. Values of sialic acid is not affected by age nor sex. Serum sialic acid is a protein-bound carbohydrate considered to be a monosaccharide and occurs in combination with other monosaccharides like galactose, galactosamine and fructose. It has been reported that human serum contains almost no free sialic acid and 90% of serum sialic acid was bound to alpha and beta globulins.¹⁸ It can be used as a measurement of the acute phase response because of the many proteins of the immune response are actually glycoproteins

and they have sialic acid as the terminal sugar on their oligosaccharide chain.²⁰ It also established a link between inflammation and glucose intolerance. Chronic activation of the innate immune system can lead to insulin resistance and abnormalities in glucose intolerance and lipid metabolism. Pregnancy has also contrasting changes in the maternal innate immune system which brings about an upsurge in multiple cytokines, granulocytes, monocytes and acute phase protein as early as first trimester.¹ With the hormonal changes in pregnancy and its addition to other conditions such as increasing age, obesity and GDM will increase the values of our inflammatory markers and these were shown in my data noting that there was an increasing trend in the levels of total sialic acid as gestational age increases and more so those with gestational diabetes. Their levels are also increased with ethnic groups. Signs of infection, intake of pyruvate containing food and ascorbic acid that will affect the results of total sialic acid were eliminated.³ In the study of Moretti *et al*, it showed that there was an increase in the levels of total sialic acid in patients with GDM which she attributed to microcirculatory abnormality in these patients. There is increased whole blood viscosity and reduced erythrocyte deformability which might cause microcirculatory alterations even in the presence of good metabolic control and of a short duration.²⁰

In this study, we also noted that total sialic acid was twice elevated among pregnant women with normal glucose tolerance at twelve weeks and thrice elevated with pregnant with IGT and GDM. No study has established a range of TSA values at twelve weeks and below. Likewise, TSA levels were three to four times elevated in both IGT and GDM both 12 and 24 weeks gestation. We ensured that patient enrolled had other co-morbid infection that could explain the elevation. Sriharan *et al* established that increased TSA levels are associated with previous diagnosis of GDM, hyperglycemia and other elements of metabolic syndrome This strengthens the theory that innate immune system is activated in pregnancy and that pregnancy is associated with insulin resistance, fat deposition, and various metabolic syndrome components such as GDM, dyslipidemia and hypertension.¹⁴

Though the mean white blood cell count was significantly different at 12 weeks it didn't show any significant variation at 24 to 28 weeks which can be attributed to small sample size. There is a physiologic leukocytosis during pregnancy which was brought about by the increased stimulation by the innate immune system giving rise to increased levels of cytokines, macrophages and acute phase reactants.¹⁰ Lao, T. *et al* studied the development of gestational diabetes in third trimester and concluded

that there is a significant change in blood count beyond the advancing age alone.²¹

C-reactive protein was higher among women with GDM when compared with IGT and those with normal glucose tolerance at all weeks of gestation. This acute phase reactant has been associated with cardiovascular disease as well as insulin resistance syndrome in nonpregnant individual. This examination can detect low inflammatory state. CRP is sensitive and it can detect as low as 0.3 mg/l in venous or whole blood.¹⁸ Our result was supported by Qui *et al* in his study showing an association of CRP with GDM risk.¹² Though this test is non-specific, there are a lot of strong datas that will associate CRP with dyslipidemia, hypertension, and diabetes mellitus.

Erythrocyte sedimentation rate is one very useful tool to detect inflammation however their usefulness decreased as newer diagnostics have come out in evaluating other inflammatory conditions. This is a simple and less expensive examination. Any condition that elevates fibrinogen levels like pregnancy, diabetes mellitus can show an increase in ESR which was shown in this study. Our study showed that ESR was significantly elevated among pregnant women with GDM when compared to those with IGT and normal glucose tolerance. ESR may give false positive and false negative results which its reliability is questionable.

Hence with this study, total sialic acid and CRP may be used as predictors for gestational diabetes. Sialic acid is less expensive than CRP in terms of cost effectiveness. And pregnant women with high levels of these may warrant close monitoring for early prevention of GDM.

RECOMMENDATIONS

It is imperative to include a sufficient sample size to determine the cut-off value of total sialic acid in predicting pregnant women who will have Gestational Diabetes. A more frequent measurement of total sialic acid and other inflammatory markers at all age of gestation will be documented for a more accurate conclusion.

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