Original Research Article

A study on role of biochemical markers in prediction of gestational diabetes mellitusa

Pratyusha[1], M.Swarnalatha[2], N.Chandraprabha[3], R.Sujatha[4*]

[1]Andhra Medical College, Visakhapatnam, Andhra Pradesh, India
[2]Associate Professor, Andhra Medical College Visakhapatnam, Andhra Pradesh, India
[3]Associate Professor, Rangaraya Medical College, Kakinada, Andhra Pradesh, India
[4]Assistant Professor, Rangaraya Medical College, Kakinada, Andhra Pradesh, India

Received: 2-11-2021 / Revised: 28-12-2021 / Accepted: 07-01-2022

Abstract

Introduction: Diabetes mellitus is a disorder of carbohydrate metabolism. It is caused by a combination of hereditary and environmental factors characterized by either inadequate secretion or inadequate action of insulin. Both pre gestational and gestational diabetes pose many risks to the mother and fetus. In addition to traditional risk factors, several biochemical markers like glycated hemoglobin HbA1c, fasting and postprandial blood sugars and inflammatory markers like c reactive protein, cytokines, pregnancy associated plasma protein-A, which are implicated in pathophysiology of GDM and involved in mechanism related to insulin resistance or chronic inflammation have been studied to predict risk of developing GDMearly[16]. **Aims:** To diagnose GDM in early trimester with the help of certain biochemical markers like Fasting blood sugar, Postprandial blood sugar, glycosylated hemoglobin HbA1C and C Peptide. **Methodology**: This is a prospective study done in 200 Pregnant women in early trimester who attended OPD in King George Hospital, Visakhapatnam. With informed consent, these pregnant women are subjected to detailed clinical examination and before 20 weeks subjected to fasting blood sugars, postprandial blood sugars, HbA1C,C – peptide estimation &were followed up with regular antenatal checkups and appropriate antenatal care and at about 24 -28 weeks of period of gestation 75 g oral glucose tolerant testwas done according to the standard protocols for testing regarding concentration and amount of glucose,fasting and timing of blood sample collection. Based on the results of this test, included pregnant women are categorized into GDM (cases) and non GDM group (controls) with cutoff value of 75g glucose tolerant test being 140 mg /dl. **Results**: The mean values of the selected biochemical markers were significantly higher in GDM cases when compared to controls.The mean FBS,PPBS, HBA1C and C-Peptide of first trimester in GDM cases were 86.76mg/dl,122.76mg/dl,5.4g%,3.4647ng/ml respectively. **Conclusion:** Gestational Diabetes mellitus is a very common global health problem which is significantly increasing universally with changing life style habits.This increasing rate and it's effect on maternal and fetal health makes the concept of EARLY DIAGNOSIS of GDM, a very crucial part to our health system .Pregnant women with fasting blood glucose more than 86.76 mg/dl, PPBS more than 122.76 mg/dl, HbA1C more than 5.4g%in first trimester, c peptide more than 3.4ng/ml have to be cautious and are at risk of developing GDM in late trimester and hence followed up carefully. The above Reference cut off values of markers included in our study are yet to be established by further studies with larger population.

Keywords: Gestational diabetes mellitus, Biochemical markers, Fasting blood sugars, postprandial blood sugars, HBa1c, c – peptide

Introduction

Diabetes mellitus is a disorder of carbohydrate metabolism.It is caused by a combination of hereditary and environmental factors characterized by either inadequate secretion or inadequate action of insulin.

According to American College of Obstetrics and Gynecology (ACOG)Gestational Diabetes Mellitus is defined as "Any degree of glucose intolerance that either commences or is first diagnosed in pregnancy "This definition includes women whose glucose tolerance will return back to normal after pregnancy and also those who will persist with glucose intolerance and develop type 2 diabetes mellitus[1,2,8].

Increased incidence of GDM is attributed to increased prevalence of obesity, metabolic syndrome, trend towards older maternal age,adoption of modern lifestyle, reducing physical activities[3,4].

Need for study

Both pre gestational and gestational diabetes pose many risks to the mother and fetus. Uncontrolled and undiagnosed GDM leads to deleterious effects on both mother and fetus. Early diagnosis and management of GDM helps to prevent fetus from exposure to hyperglycemia and thus prevent many fetal effects - cardiac anomalies, neural tube defects etc, sudden intrauterine demise andothers and develop fewer complications like polyhydramnios, prematurity and macrosomia[11].

At present diagnosis of GDM is based on 75gram Oral Glucose Tolerance Test done at first ANC &between 24 to 28 weeks. Early diagnosis of GDM by biochemical markers prior to second trimester would be beneficial to prevent deleterious effects of GDM[15].

Biomarkers are the substances in the body which are quantified and assessed to represent a physiologic or pathological or pharmacological response to a therapeutic intervention. They are used either to assess the risk of developing a disease or used as a screening tool.In addition to traditional risk factors,several biochemical markers like glycated hemoglobin HbA1c, fasting and postprandial blood sugars and inflammatory markers like c reactive protein, cytokines, pregnancy associated plasma protein -A which are implicated in pathophysiology of GDM and involved in mechanism related to insulin resistance or chronic inflammation have been studied topredict risk of developing GDMearly[16].

HbA1c has less inter laboratory variations compared to plasma glucose levels collected during OGTT, less intra individual variability as it is not effected by diurnal variations, meals, fasting, acute stress or drugs that influence glucose metabolism[10].

Connecting peptide (C-Peptide) produced in equi-molar concentration to insulin ,is known to be a useful marker of beta cell function and can be used to assess endogenous insulin secretion[61]. C-Peptide is preferable to insulin as insulin is rapidly destroyed by enzyme

*Correspondence
Dr. R.Sujatha
Assistant Professor, Rangaraya Medical College, Kakinada, Andhra Pradesh, India.

insulinase of liver, placenta and kidney and it's half-life is 5minutes whereas whereas C-Peptide is not destroyed as rapidly as insulin and its half-life is longer(about 30-35min).

Aims of the study

To diagnose GDM in early trimester with the help of certain biochemical markers like Fasting blood sugar, postprandial blood sugar, glycosylated hemoglobin HbA1C, C-peptide.

Materials & methods

Study design

Prospective observational study.

Study period

November2020 to October 2021 in department of Obstetrics & Gynecology, Andhra Medical college

Study Setting

Department of Obstetrics& Gynecology, King George Hospital, Visakhapatnam.

Study population

Antenatal women in early trimester before 20 weeks period of gestation.

Inclusion criteria

Pregnant women prior to 20 weeks period of gestationand women with history of GDM in previous pregnancies are included and women who gave valid informed consent are included.

Exclusion criteria

- Pregnant women after 20weeks.
- known case of diabetes mellitus.
- Patients with chronic medical disorders were excluded.
- Patients with low Hemoglobin levels and hemoglobin opathies and
- patients on cholesterol lowering drugs were also excluded from the study.

Methodology

This is a prospective study, done in Pregnant women in early trimester who attended OPD in King George Hospital,Visakhapatnam. With informed consent, these pregnant women are subjected to detailed clinical examination and before 20 weeks subjected to fasting blood sugars, postprandial blood sugars, HbA1C,C–peptide& were followed up with regular antenatal checkups and appropriate antenatalcare and at about 24 -28 weeks of period of gestation 75 g oral glucose tolerant testwas done according to the standard protocols for testing regarding concentrationand amount of glucose ,fasting and timing of blood sample collection.Based on the results of this test, included pregnant women are categorized into

GDM (cases)and non GDM group (controls) with cutoff value of 75g glucose tolerant test being 140 mg /dl.

Observations and results

With due considerations of all inclusion and exclusion criteria, a total of 200 pregnant women were included in the study

Table 1: Age group of the study population

AGE GROUP	GDM		NON-GDM		TOTAL	
	N	%	N	%	N	%
18-20	0	0.0	3	1.6	3	1.5
21-25	13	76.5	155	84.7	168	84.0
26-30	4	23.5	25	13.7	29	14.5
TOTAL	17	100.0	183	100.0	200	100.0

CHI SQUARE = 1.449, P VALUE = 0.485 (NS)

In our study population, the mean age of the study population was 24.18 in GDM group and 23.41 in non GDM group. Below the age group of 20 years, occurrence of diabetes in pregnancy is none in our study.

Table 2: Parity in the study population

GRAVIDA	GDM		NON-GDM		TOTAL	
	N	%	N	%	N	%
PRIMI	4	23.5	92	50.3	96	48
G2	7	41.1	66	36.1	73	36.5
G3	6	35.2	19	10.4	25	12.5
G4	0	0.0	4	2.2	4	2.0
G5	0	0.0	2	1.1	2	1.0
TOTAL	17	100.0	183	100.0	200	100.0

CHI SQUARE = 10.709, P VALUE = 0.030 (S)

In our study population, about 23.5% ofGDM group were primigravida and percentage of non GDM cases in primigravida - 50.3% and majority of GDM casesie 76.3% seen in parous women and whereas percentage of non GDM cases in parous women- 46.5% with P value of 0.03 implies that the occurrence of GDM in Parous women is significant .

Table 3: BMI of study population

BMI	GDM		NON-GDM		TOTAL	
	N	%	N	%	N	%
18.5-24.9	12	70.6	178	97.3	190	95.0
25.0-29.9	5	29.4	5	2.7	10	5.0
TOTAL	17	100.0	183	100.0	200	100.0

CHI SQUARE = 23.309, P VALUE = 0.001 (S)

In our study population, About 29.4% of cases in GDM group and 2.7%in non GDM group had BMI >25, implying that there is increased risk of GDM in individuals with higher BMI

Table 4: Family History

FAMILY HISTORY	GDM		NON-GDM		TOTAL	
	N	%	N	%	N	%

YES	4	23.5	37	20.2	41	20.5
NO	13	76.5	146	79.8	159	79.5
TOTAL	17	100.0	183	100.0	200	100.0

CHI SQUARE = 0.105, P VALUE = 0.746 (NS)

In our study population, 23.5% in GDM Group and 20.20% in non-GDM Group showed positive family history of Diabetes.

Table 5: FBS in first trimester Sub Group

FBS	GDM		NON-GDM		TOTAL	
	N	%	N	%	N	%
<75	0	0.0	55	30.1	55	27.5
76-85	3	17.6	91	49.7	94	47.0
>85	14	82.4	37	20.2	51	25.5
TOTAL	17	100.0	183	100.0	200	100.0

CHI SQUARE = 32.065, P VALUE = 0.001 (S)

In our study population , about 82.4% of GDM cases showed FBS of first trimester >85mg/dl. From the above results, Out of 17 GDM Cases 14 has FBS more than or equal to 85mg/dl. So, the cut-off value of fasting blood sugar in first trimester to predict GDM is taken as 85mg/dl in our study.

Table 6: Results of FBS In first trimester in our study population

FBS	GDM		NON-GDM		TOTAL	
	N	%	N	%	N	%
<85	3	17.6	142	77.6	145	72.5
>85	14	82.4	41	22.4	55	27.5
TOTAL	17	100.0	183	100.0	200	100.0

CHI SQUARE = 28.039, P VALUE = 0.001 (S)

In our study population , about 82.4% of GDM cases showed FBS of first trimester >85mg/dl whereas only 22.4% of non- GDM cases showed FBS >85 mg/dl with p **value of 0.001 being statistically significant for the prediction of GDM.**

Table 7: PPBS Sub Group

PPBS	GDM		NON-GDM		TOTAL	
	N	%	N	%	N	%
<95	0	0.0	2	1.1	2	1.0
96-105	0	0.0	28	15.3	28	14.0
106-115	3	17.6	88	48.1	91	45.5
116-120	1	5.9	30	16.4	31	15.5
>120	13	76.5	35	19.1	48	24.0
TOTAL	17	100.0	183	100.0	200	100.0

CHI SQUARE = 28.377, P VALUE = 0.001 (S)

In our study population , about 76.5% of GDM cases showed PPBS of first trimester >120mg/dl. From the above results, Out of 17 GDM Cases 13 has PPBS more than or equal to 120mg/dl. So, the cut-off value of postprandial blood sugar in first trimester to predict GDM is taken as 120mg/dl in our study.

Table 8: Results of PPBS In first trimester in our study population

PPBS	GDM		NON-GDM		TOTAL	
	N	%	N	%	N	%
<120	4	23.5	146	79.8	150	75.0
>120	13	76.5	37	20.2	50	25.0
TOTAL	17	100.0	183	100.0	200	100.0

CHI SQUARE = 26.251, P VALUE = 0.001 (S)

In our study population , about 76.5% of GDM cases showed PPBS of first trimester >120mg/dl whereas only 20.2% of non- GDM cases showed PPBS>120 mg/dl with p value of 0.001 being statistically significant for the prediction of GDM.

Table 9: HbA1c SUB GROUP

HbA1c	GDM		NON-GDM		TOTAL	
	N	%	N	%	N	%
<4.5	1	5.9	90	49.2	91	45.5
4.6-5.5	3	17.6	89	48.6	92	46.0
5.6-6.5	13	76.5	4	2.2	17	8.5
TOTAL	17	100.0	183	100.0	200	100.0

CHI SQUARE = 110.64, P VALUE = 0.001 (S)

In our study population , about 76.5% of GDM cases showed HbA1c of first trimester >5.6g%. From the above results, Out of 17 GDM Cases 13 has HbA1c more than or equal to 5.6g%. So, the cut-off value of HbA1c in first trimester to predict GDM is taken as 5.6g% in our study

Table 10: HbA1c GROUP

HbA1c	GDM		NON-GDM		TOTAL	
	N	%	N	%	N	%
<5.5	4	23.5	175	95.6	179	89.5
>5.5	13	76.5	8	4.4	21	10.5
TOTAL	17	100.0	183	100.0	200	100.0

CHI SQUARE = 86.043, P VALUE = 0.001 (S)

In our study population , about 76.5% of GDM cases showed HbA1c of first trimester >5.6g% whereas only 2.2% of non- GDM cases showed HbA1c >120 5.6g% with p value of 0.001 being statistically significant for the prediction of GDM.

Table 11: C PEPTIDE Sub Group

C PEPTIDE	GDM		NON-GDM		TOTAL	
	N	%	N	%	N	%
<2	3	17.6	65	35.5	68	34.0
2.1-3.0	3	17.6	90	49.2	93	46.5
3.1-4.0	4	23.5	23	12.6	27	13.5
>4	7	41.2	5	2.7	12	6.0
TOTAL	17	100.0	183	100.0	200	100.0

CHI SQUARE = 44.488, P VALUE = 0.001 (S)

In our study population , about 64.7% of GDM cases showed C Peptide of first trimester >3.1ng. From the above results, Out of 17 GDM Cases 11 has C Peptide more than or equal to 3.1ng. So, the cut-off value of C Peptide in first trimester to predict GDM is taken as 3.1ng in our study

Table 12: C PEPTIDE Group

C PEPTIDE (ng/ml)	GDM		NON-GDM		TOTAL	
	N	%	N	%	N	%
<3	6	35.3	154	84.2	160	80.0
>3	11	64.7	29	15.8	40	20.0
TOTAL	17	100.0	183	100.0	200	100.0

CHI SQUARE = 23.208, P VALUE = 0.001 (S)

In our study population , about 64.7% of GDM cases showed C Peptide Of first trimester>3.1ng/ml whereas only 15.3% of non- GDM cases showed C Peptide >3.1ng/ml with p value of 0.001 being statistically significant for the prediction of GDM.

Table 13: Mode of delivery

MODE OF DELIVERY	GDM		NON-GDM		TOTAL	
	N	%	N	%	N	%
LSCS	13	76.5	62	33.9	75	37.5
NVD	4	23.5	121	66.1	125	62.5
TOTAL	17	100.0	183	100.0	200	100.0

CHI SQUARE = 12.039, P VALUE = 0.001 (S)

In our study population, about 76.5 % of GDM had LSCS and 33.9% of non-GDM Cases had LSCS.

Table 14: Birth Weight

BIRTH WEIGHT	GDM		NON-GDM		TOTAL	
	N	%	N	%	N	%
<3 KG	2	11.8	151	82.5	153	76.5
>3 KG	15	88.2	32	17.5	47	23.5
TOTAL	17	100.0	183	100.0	200	100.0

CHI SQUARE = 43.309, P VALUE = 0.001 (S)

In our study Population, about 88.2 % of GDM and 17.5% of non- GDM cases have birthweight >3kg.

Table 15: APGAR at birth

APGAR at birth	GDM		NON-GDM		TOTAL	
	N	%	N	%	N	%
4-6	0	0.0	1	0.5	1	0.5
6-8	3	17.6	41	22.4	44	22.0
8-10	14	82.4	141	77.0	155	77.5
TOTAL	17	100.0	183	100.0	200	100.0

CHI SQUARE = 0.309, P VALUE = 0.857 (NS)

Table 16: List of Mean values of variables of this study

VARIABLE	GDM (N=17)		NON-GDM (N=183)		P VALUE
	MEAN	SD	MEAN	SD	
AGE	24.18	2.675	23.41	2.138	.168
BMI	24.082	2.231	21.506	1.5460	.001

Table **17: List of mean Values of variables of this study(continuation)**

VARIABLE	GDM (N=17)		NON-GDM (N=183)		P VALUE
	MEAN	SD	MEAN	SD	
FBS	86.76	4.381	78.58	6.427	.001
PPBS	122.76	6.960	112.78	6.933	.001
HbA1c	5.482	.4246	4.625	.3969	.001
C PEPTIDE	3.4647	1.21241	2.3711	1.07216	.001
BIRTH WEIGHT	3.3765	.34192	2.7866	.26545	.001

Discussion

Incidence

Incidence of GDM in our study is 8.3%.Prevalence of GDM varies in various countries depending on ethnicity, diagnostic criteria, screening strategies and other different population characteristics.

Age and GDM

Mean age of GDM in our study population is 24.18 years and is in agreement with study conducted by Shaly et al 2018.

Various studies showed that there is a progressive increase in incidence of GDM with increasing age and more predominant in pregnant women of age group more than 30 years[17-20]

BMI and GDM

In our study mean BMI in GDM population is 22.89. In our study population, majority of GDM cases had normal BMI (less than 25kg/m2) and 29.4% of GDM were overweight and 2.9% of non GDM cases were overweight with p value 0.001 showing significant association between overweight/obesity and GDM. Similar results are found in Shaly C.M.et al 2018.

Parity and GDM

Many of the pregnant women who are GDM in our study are parous women constituting 76.3% which is comparable with Vijayameenakshi et al study.

Family history of diabetes

In our study population, 23.5% of GDM and 20.2% of non GDM cases showed positive family history with p value 0.746 which is not significant. Similar findings obtained in study conducted by Vijayameenakshi et al.

Biochemical markers and GDM

With tremendously increasing incidence of GDM in modern era, it is very important to have appropriate screening techniques for early diagnosis and prevention of complications. However, present screening tests as recommended by IADSPG, HAPO and ACOG includes glucose tolerance tests at 24 – 28 weeks . Glucose tolerant tests when done in early trimesters may not diagnose underlying disease and hence usually done at 24 to 28 weeks.

Diagnosis of the disease in second trimester can lead to various short and long term effects to mother, fetus and later life of the child.

Hence it is important to understand the pathophysiology of gestational diabetes mellitus and study on various inflammatory and insulin related markers to diagnose gestational diabetes mellitus even before its occurrence to prevent short and long term consequences.

Various biochemical markers include fasting blood sugars, glycosylated hemoglobin, HOMA-IR, fasting insulin levels, c-peptide, sex hormone binding protein ,leptin, adiponectin, inflammatory markers like c reactive protein, highly sensitive c reactive protein, Tumor necrosis factor, interleukin-6.[21-25]

Various studies have been taking place in this field and many markers have been extensively studied.

In our study population, we performed tests to study were- role of fasting blood sugars, postprandial sugars , HbA1C , c peptide in early trimester to predict GDM.

1. **Fasting Blood Sugar:**
   In our study population, mean FBS value in GDM population was 86.76mg/dl and is significantly higher to predict GDM. Similar findings are found in Hatice Kansu-Celik et al study in 2021,Fahami et al , Riskin-Mashiah et al & Jain – wei Laing et al in 2021.It is observed that fasting blood sugars are better in prediction of GDM when compared to traditional risk factors like age, Obesity and positive family history.
2. **Postprandial Blood Sugar:**In our study population, mean PPBS value in GDM group was 122.76 mg/dl and mean PPBS in non GDM group was 112.78mg/dl with p value 0.001 and shows that PPBS>120mg/dl in first trimester has good positive prediction of occurrence of GDM in late trimester .
   In various studies to establish predictive role of biochemical markers in GDM , many markers have been extensively studied and among them role of fasting blood sugars and glycosylated hemoglobin have been included in various studies . However postprandial sugars are not so extensively studied on par with fasting blood sugars and it's predictive role of GDM yet to be studied further.
3. **Glycosylated Hemoglobin**
   In our study population, mean value of HbA1C in GDM group was 5.5g% & is comparable with many studies conducted on bio markers[29-32]
   HbA1c levels above 5.6% had a diagnostic accuracy of 62.66%.HbA1C of first trimester was an independent risk factor and value >5.9% had significantly increased risk of GDM
4. **C-PEPTIDE**

In our study population, mean value of c peptide is 3.46 ng/ml and in non GDM group is 2.37ng/ml with p value 0.001 and is statistically significant to predict GDM. C peptide is a potential marker to predict insulin resistance and thus GDM. It is elevated in hyperinsulinemia state and thus help to differentiate from type 1 and type 2 diabetes mellitus. Estimation of C peptide is done in laboratories by immune chemical method and hence involves various interferences and the range of references for cut off value are highly variable depending on the reagent, analyser used and fasting state of the person. Hence, studies has to be conducted in larger populations to get the reference cut off values to predict GDM. In our study population majority of GDM cases had cesarean deliveries in about 76.5% cases. There is increased rate of cesarean delivery due to big baby, CPD and emergency cesarean for failed induction, delayed progression, decreased fetal movements[26-28]

Summary

- Incidence of GDM is 8.3%
- Mean age group in GDM is 24.18 years
- Mean BMI in GDM group is 24.08
- 23.5% of GDM cases had family history of diabetes mellitus
- 76.3% of GDM cases were parous women
- Mean FBS of first trimester in GDM group is86.76 mg/dl +/- 4.3mg/dl.
- Mean PPBS of first trimester in GDM group is 122.76 mg/dl+/- 6.9 mg/dl
- Mean HbA1C of first trimester in GDM group is 5.4%+/-0.4%
- Mean c peptide of first trimester in GDM group is 3.4647+/-1.21
- 76.5% of GDM cases had cesarean deliveries
- 88.2% of GDM cases had birth weight >3kg with mean birth weight of about 3.3765+/-0.34

Conclusion

- Gestational Diabetes mellitus is a very common global health problem which is significantly increasing universally with changing life style habits. This increasing rate and it's effect on maternal and fetal health makes the concept of EARLY DIAGNOSIS of GDM, a very crucial part to our health system .
- On par with this, various bio markers which are involved in the pathogenesis of gestational Diabetes have been studied extensively to establish the diagnostic role in early diagnosis of GDM
- However, so far none of the bio markers have demonstrated adequate results , so as to include into our routine screening methods.
- Studies including novelbio markers in the areas of genetic and epigenetic field in relation to GDM and its applications for predictability have been emerging as an exciting area for future research and development.
- Cost effectiveness and universal accessibility of the testing methodology is the most important thing for a marker to be included in our health system in addition to its predictability of the disease.
- In pregnant women with fasting blood glucose more than 86.76 mg/dl, PPBS more than 122.76 mg/dl, HbA1C more than 5.4g%in first trimester, c peptide more than 3.4ng/ml have to be cautious and are at risk of developing GDM in late trimester and hence followed up carefully.
- The above Reference cut off values of markers included in our study are yet to be established by further studies with larger population[33-36]

References

1. Metzger BE, Coustan DR, Committee O. Summary and recommendations of the fourth international workshop-conference on gestational diabetes mellitus. Diabetes Care. 1998;21:B161.

2. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol. 2018 Feb;131(2):e49-e64.
3. Simmons D, editor. Epidemiology of Diabetes in Pregnancy. In: McCance DR, Maresh M, Sacks DA, eds. A Practical Manual of Diabetes in Pregnancy. Chichester, UK: John Wiley & Sons; 2017. p. 1-16.
4. Brink HS, van der Lely AJ, van der Linden J. The potential role of biomarkers in predicting gestational diabetes. Endocr Connect. 2016;5:R26–34.
5. Mills JL, Baker L, Goldman AS. Malformations in infants of diabetic mothers occur before the seventh gestational week: implications for treatment. Diabetes 1979;28:292–3.
6. Chorell E, Berntorp K, Puhkala J, Luoto R, et al. Pregnancy to postpartum transition of serum metabolites in women with gestational diabetes. Metabolism. 2017;72:27–36.
7. Kebapcilar L. Is the Mean Platelet Volume a Predictive Marker of a Low Apgar Score and Insulin Resistance in Gestational Diabetes Mellitus? A Retrospective Case-Control Study. J Clin Diagn Res. 2016;10:C06–10.
8. Pons RS, Rockett FC, de Almeida Rubin B, Oppermann MLR, Bosa VL. Risk factors for gestational diabetes mellitus in a sample of pregnant women diagnosed with the disease. DiabetolMetabSyndr. 2015;7 Suppl 1:A80.
9. Kwon EJ, Kim YJ. What is fetal programming?: a lifetime health is under the control of in utero health. ObstetGynecol Sci. 2017;60:506.
10. Guariguata L, Linnenkamp U, Beagley J, Whiting D, Cho N. Global estimates of the prevalence of hyperglycaemia in pregnancy. Diabetes Res Clin Pract. 2014;103(2):176–85.
11. Gasim T. Gestational diabetes mellitus: maternal and perinatal outcomes in 220 Saudi women. Oman Med J. 2012;27(2):140.
12. Wendland EM, Torloni MR, Falavigna M, Trujillo J, Dode MA, Campos MA, et al. Gestational diabetes and pregnancy outcomes-a systematic review of the World Health Organization (WHO) and the International Association of Diabetes in Pregnancy study groups (IADPSG) diagnostic criteria. BMC Pregnancy Childbirth. 2012;12(1):23.
13. Coustan DR, Lowe LP, Metzger BE . The hyperglycemia and adverse pregnancy outcome (HAPO) study: can we use the results as a basis for change? J Matern Fetal Neonatal Med 2010; 23 (3): 204–209.
14. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. Am J ObstetGynecol 1982; 144 (7): 768–773.
15. WHO. Expert Committee on Diabetes Mellitus: second report. World Health Organ Tech Rep Ser 1980; 646: 1–80.
16. Rodrigo N, Glastras S. The Emerging Role of Biomarkers in the Diagnosis of Gestational Diabetes Mellitus. J Clin Med. 2018;7:120.
17. Kopylov AT, Papysheva O, Gribova I, Kotaysch G, Kharitonova L, Mayatskaya T, et al. Molecular pathophysiology of diabetes mellitus during pregnancy with antenatal complications. Sci Rep. 2020;10:19641.
18. Biomarkers Definitions Working Group. Atkinson A.J., Jr., Colburn W.A., DeGruttola V.G., DeMets D.L., Downing G.J., Hoth D.F., Oates J.A., Peck C.C., Schooley R.T., et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clin. Pharmacol. Ther. 2001;69:89–95.
19. Vasan R.S. Biomarkers of cardiovascular disease: Molecular basis and practical considerations. Circulation. 2006;113:2335–2362.
20. Smirnakis K.V., Martinez A., Blatman K.H., Wolf M., Ecker J.L., Thadhani R. Early Pregnancy Insulin Resistance and Subsequent Gestational Diabetes Mellitus. Diabetes Care. 2005;28:1207–1208.
21. Grewal E., Kansara S., Kachhawa G., Ammini A.C., Kriplani A., Aggarwal N., Gupta N., Khadgawat R. Prediction of gestational diabetes mellitus at 24 to 28 weeks of gestation by using first-trimester insulin sensitivity indices in Asian Indian subjects. Metabolism. 2012;61:715–720.
22. Bito T., Foldesi I., Nyari T., Pal A. Prediction of gestational diabetes mellitus in a high-risk group by insulin measurement in early pregnancy. Diabet. Med. 2005;22:1434–1439.
23. Ozgu-Erdinc A.S., Yilmaz S., Yeral M.I., Seckin K.D., Erkaya S., Danisman A.N. Prediction of gestational diabetes mellitus in the first trimester: Comparison of C-reactive protein, fasting plasma glucose, insulin and insulin sensitivity indices. J. Matern. Fetal Neonatal Med. 2015;28:1957–1962.
24. Smirnakis K.V.,Thadhani R., Ecker J.L. Predicting gestational diabetes: Choosing the optimal early serum marker. Am. J. Obstet. Gynecol. 2007;196:410.e1–410.e6.
25. Corcoran S.M., Achamallah N., O'Loughlin J., Stafford P., Dicker P., Malone F.D., Breathnach F. First trimester serum biomarkers to predict gestational diabetes in a high-risk cohort: Striving for clinically useful thresholds. Eur. J. Obstet. Gynecol. Reprod. Biol. 2018;222:7–12.
26. Villar J.,Castillo P., Menendez R., Repke J.T. Effect of fat and fat-free mass deposition during pregnancy on birth weight. Am. J. Obstet. Gynecol. 1992;167:1344–1352.
27. Herrera E. Lipid metabolism in pregnancy and its consequences in the fetus and newborn. Endocrine. 2002;19:43–55.
28. Alvarez J.J., Montelongo A., Iglesias A., Lasuncion M.A., Herrera E. Longitudinal study on lipoprotein profile, high density lipoprotein subclass, and postheparin lipases during gestation in women. J. Lipid Res. 1996;37:299–308.
29. Herrera E., Ortega-Senovilla H. Disturbances in lipid metabolism in diabetic pregnancy–Are these the cause of the problem? Best Pract. Res. Clin. Endocrinol. Metab. 2010;24:515–525.
30. Ryckman K., Spracklen C., Smith C., Robinson J., Saftlas A. Maternal lipid levels during pregnancy and gestational diabetes: A systematic review and meta-analysis. BJOG. 2015;122:643–651.
31. Perichart-Perera O., Muñoz-Manrique C., Reyes-López A., Tolentino-Dolores M., Espino Y Sosa S., Ramírez-González M.C. Metabolic markers during pregnancy and their association with maternal and newborn weight status. PLoS ONE. 2017;12:e0180874.
32. Mossayebi E., Arab Z., Rahmaniyan M., Almassinokiani F., Kabir A. Prediction of neonates' macrosomia with maternal lipid profile of healthy mothers. Pediatr. Neonatol. 2014;55:28–34.
33. Jin W.Y., Lin S.-L., Hou R.-L., Chen X.-Y., Han T., Jin Y., Tang L., Zhu Z.-W., Zhao Z.-Y. Associations between maternal lipid profile and pregnancy complications and perinatal outcomes: A population-based study from China. BMC Pregnancy Childbirth. 2016;16:60.
34. Yang Y.D., Zhai G.R., Yang H.X. Factors relevant to newborn birth weight in pregnancy complicated with abnormal glucose metabolism. Zhonghua Fu Chan Ke Za Zhi. 2010;45:646–651.
35. Syngelaki A., Visser G.H.A., Krithinakis K., Wright A., Nicolaides K.H. First trimester screening for gestational diabetes mellitus by maternal factors and markers of inflammation. Metabolism. 2016;65:131–137.
36. Wolf M., Sandler L., Hsu K., Vossen-Smirnakis K., Ecker J.L., Thadhani R. First-trimester C-reactive protein and subsequent gestational diabetes. Diabetes Care. 2003;26:819–824.

Conflict of Interest: Nil Source of support: Nil