Association of Body Mass Index with Activin-A and Inhibin-A in Gestational Diabetic Women

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Abstract

Objective: The objective of the study was to assess the association of body mass index (BMI) with Activin-A and Inhibin-A (biomarkers) irrespective to age in women with gestational diabetes mellitus (GDM).

Methods: This study was a case-controlled study, in which sixty (60) diagnosed cases of gestational diabetic women with and without obesity and thirty (30) pregnant women without diabetes or any other complications were included in the study after taking informed written consent. The duration of the study was from January 2018 to June 2018. The enrolled participants were ninety (90) who were fulfilling the criteria in the duration of the study. Participants were placed into three groups A, B and C. In group A, thirty (30) pregnant females without complications, in group B thirty (30) non-obese pregnant women with gestational diabetesand in group C thirty (30) obese pregnant females with gestational diabetes mellitus (GDM). The biophysical parameters including weight, height and blood pressure were measured through standard protocols. Blood tests for biomarkers Activin-A and Inhibin-A levels were measured through Human Activin-A enzyme-linked immunosorbent assay(ELISA) kit and Human Inhibin-A ELISA kit respectively.

Results: The results of the study revealed that thebiophysical markers Actin-A and Inhibin-A had associations with gestational diabetes, the significant (p-value<0.05) association was observed between Activin-A and body mass index but Inhibin-A had insignificant association with it. However, the levels of both biomarkers (Activin-A and Inhibin-A) were found to be raised in both obese and non-obese gestational diabetic women when compared with normal pregnant women. The secondary outcome of the study is, there is significant (p-value>0.05) relation between age and body mass index of obese GDM.

Conclusion: The study concluded that level of Activin-A were raised significantly (p-value>0.05) in obese and non-obese gestational diabetic women as compare to normal pregnant women and non-significant increases in inhibin-A was observedin obese and non-obese gestational diabetic women as compare to normal pregnant women. A secondary outcome was, that there is significant (p-value>0.05) association found between body mass index and age of the pregnant women.

Keywords: Activin-A, body mass index, gestational diabetes mellitus, inhibin-A, preeclampsia

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Introduction

Women with gestational diabetes have high blood sugar levels, particularly after 20 weeks of gestation, but have not previously been diagnosed as diabetics. Gestational diabetes is the result of the insulin receptors not functioning properly and generally resolves once the baby is born. Gestational diabetes mellitus (GDM) is medical complication in pregnancy, its incidence is 14% of normal pregnancies[1]. Women with GDM (gestational diabetes mellitus) are prone to develop type II diabetes mellitus and the offspring are also at increased risk to develop short and long term complications like complications of labour (obstructive labour leads to foetal anoxia, shoulder dystocia causes trauma to brachial plexus etc.) obesity, type 2 diabetes, and metabolic syndrome[2]. The intrauterine environment of hyperglycaemic mother causes epigenetic

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changes in the foetus that may contribute to metabolic disorders; the occurrence of obesity is increasing globally. It is a serious health problem which leads to increased frequency of cardiac, metabolic disorders and orthopaedic problems in future[3].

Obesity is based on body mass index (BMI). Body mass index is a measure of "body fatness" basically, calculated from height and weight of adult men and women. BMI categories are; Underweight <18.5, Normal weight 18.5 - 24.9, Overweight = 25 - 29.9; In obesity BMI is 30 or greater[1]. It has also been observed that women having BMI of more than 30 kg/m^2 is one of the important aspects for the occurrence of gestational diabetes and preeclampsia[4].

Globally the incidence of gestational diabetes mellitus (GDM) is on a rising trend, approximately 90% of diabetic cases were considered as GDM among pregnant women. Maternal hyperglycemia and foetal macrosomia were the two pathologies diagnosed as the most common complications that occurred in GDM (gestational diabetes mellitus)[3].

Obese pregnant women with BMI of around >30 kg/m² encountered the likelihood of preeclampsia thrice in contrast to women with normal BMI between (18.5- 25.0 kg/m^2)[5].

Inhibin and activin are part of the transforming growth factor beta (TGF-ß), family of cytokines[6], and are known for their role in regulating follicle stimulating hormone (FSH) secretion, where inhibin inhibits and activin activates secretion. These protein regulators play a vital role in regulating FSH (follicle stimulating hormone), which acts synergistically with luteinizing hormone (LH) in reproduction. Activin and inhibin are produced by the placenta during pregnancy. Their levels are increased in the serum of preeclamptic women in contrast with normal gestational aged women[7].

Activin were originally discovered in ovarian fluid and was found to stimulate the biosynthesis and secretion of FSH from pituitary cells, it has since been found to be involved in several important biological activities, such as the tissue development and functions of pancreatic endocrine cells. Activin acts to stimulate FSH hormone necessary during pregnancy and is more abundant in obese people. They also have an influence in the induction of apoptosis, metabolism, endocrine, homeostasis, bone growth, fibrosis, inflammation, neurogenesis, tubulogenic of endothelial cells, and carcinogenesis in several organs. The importance of activin to a wide variety of human physiological mechanisms makes it an important drug target. When activin is secreted, its availability to be active and bind to its receptors can be blocked by other activin-binding proteins such as inhibin and follistatin, therefore, it works more actively in them. It can also be considered as a regulator of lipid and glucose metabolism with significant influence on foetal growth. It controls several cellular actions including glucose homeostasis by increasing glucose dependent insulin secretion and enhanced beta cell proliferation[8].

Inhibin alpha, has the opposite effect of activin. It also inhibits the biosynthesis and secretion of FSH, acting as an antagonist to activin. Inhibins can be found in a wide range of tissues, and although they were originally found in the ovary (granulosa cells) and testis (sertoli cells), they have also been found in the brain and placenta[9].

It was observed that the levels of Activin-A and Inhibin-A were found to be raised in gestational diabetic pregnancies and their raised levels in third trimesters particularly, can eventually lead to pre clampsia. This might be due to the fact that acute feto-placental hypoxia triggers the release of activin, increasing the probability that activin may be considered as a compensating marker of feto-placental compromise. Therefore, the levels of activin were supposed to be raised in preeclamptic women[10,11]. Therefore, advance research is required to prove the insight that GDM and preclampsia both have common etiologic pathway. Most of the pregnancy consequences appear to share common conditions for both the diseases, suggesting that they might share same pathophysiology as well. However, studies till now didn't contrast relationships be-

tween biomarkers and risk factors related to GDM, preeclampsia or both among pregnant women. In this study we are comparing the levels of activin-A and inhibin-A in healthy normal pregnancy and in gestational diabetes mellitus with or without obesity, to provide better understanding of its relation with its complications and encourage researchers and clinicians to line up the screening strategies for prevention of complications for GDM (gestational diabetes mellitus) in pregnant women.

Subjects and Methods

The study was a case control study, carried out at the Department of Physiology, Basic Medical Science Institute (BMSI), Jinnah Postgraduate Medical Centre (JPMC) Karachi, in collaboration with the Department of Gynaecology and Obstetrics, JPMC Karachi. The study duration was from January 2018 till June 2018, after approval of synopsis and obtaining ethical permission from Institutional Review Board (IRB) of BMSI, JPMC Karachi, and from head of Gynaecology and Obstetrics department, JPMC Karachi. Participants who attended the OPD for routine antenatal check-up were selected. Sample size was calculated through online software (http://openepi.com/Menu/OE_Menu.htm), after taking prevalence 5.6%[12] and 95% confidence interval with bond of error 5%. The sample size was ninety (90). Participants were recruited after fulfilling the selection criteria out of which, thirty (30) were normal pregnant females, thirty (30) were non-obese pregnant females with GDM and thirty (30) were obese pregnant females with GDM. A written consent was taken from each participating subject. The acquired data was recorded as per designed format on the prescribed questionnaire. Inclusion criteria for cases included, gestational age more than 20 weeks, diagnosed gestational diabetic patients with or without obesity and for controls; normal healthy pregnant females of more than 20 weeks of gestation, without other medical problems. Like known hypertensive, type 1 and type 2 diabetes mellitus, thyroid problems and any systemic diseases like renal or hepatic diseases were excluded from the study. The participants were placed in three groups, Group A, included 30 normal pregnant women, Group B consisted of 30 non-obese patients of GDM while Group C consisted of 30 obese patients of GDM (gestational diabetes mellitus) on the basis of BMI (body mass index) being more than 30.

The biophysical parameters the weight was measured in kilogram through digital platform whereas the height was measured in foot by stadiometer, which was further converted into meters. The BMI was then calculated by dividing the individual's weight in kilograms (kg) with the square of his or her height in meters (m). BMI 18.5 - 24.9 as normal weight, 25 - 29.9 as overweight (non-obese) BMI 30 was considered as obese (ACOG, 2013). The blood pressure was measured by mercury sphygmomanometer (Certeza CR-2002L), and the biomarkers including Activin-A and Inhibin-A levels were measured through Human Activin-A enzyme-linked immunosorbent assay (ELISA) kit, and Human Inhibin-A ELISA kit respectively.

Data was statistically analysed through IBM SPSS software version 20 with the help of one-way analysis of variance (ANOVA) analysis, Tukey's HSD test, independent sample t-test and Pearson correlation analysis by considering p-values ≤ 0.05 as a significant.

Results

In Table 1, the baseline characteristics of the 90 study participants were depicted as mean and SD, divided into three groups A, B and C. The age of participants has non-significant difference in all three groups (in group A 25.70 ± 5.45, in group B 30.93 ± 2.61, in group C 29.87 ± 1.91). In weight of all three groups there was significant (p-values ≤ 0.05) difference and in group C significant difference with relation to A and B (in group A 56.70 ± 5.83, group B 60.10 ± 3.13, in group C 96.50 ± 3.14). There was non-significant difference regarding height of all three groups (in group A 2.60 ± 0.14, in group B 2.56 ± 0.09, in group C 2.56 ± 0.08). Body Mass Index showed significant difference in all three groups (in group A 21.60 ± 1.28, in group B

24.83 ± 0.60, in group C 37.73 ± 2.10). Regarding gestational period, there was non-significant difference in all three groups (in group A 25.07 ± 1.01, in group B 25.90 ± 1.09, in group C 25.50 ± 1.31).The baseline characteristics showed in group B and group C, that is GDM obese and non-obese groups respectively, the age and BMI in group B (30.93 ± 2.61, 24.83 ± 0.60) and in group C (29.87 ± 1.91, 37.73 ± 2.10).

In Table 2, the levels of biomarkers of groups A, B and C depicted as mean and SD (standard of deviation). Groups B and C showed a significant (p-value >0.05) increased level of Actin-A to group A of normal healthy pregnant women i.e. (6.35 ± 1.03, in group B 8.74 ± 0.69, in group C 4.58 ± 1.25). and inhibin-A level of Group B and C showed non-significant increase than group A (in group A 206.70 ± 15.83, in group B 207.33 ± 17.33, in group C 211.35 ± 19.04).

Table 1. Baseline Characteristics of Participants

Parameters	Group					
	A		B		C	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	25.70	5.45	30.93	2.61	29.87	1.91
Weight (kg)	56.70	5.83	60.10	3.13	96.50*	3.14
Height (m)	2.60	0.14	2.56	0.09	2.56	0.08
Body Mass Index (kg/m^2)	21.60	1.28	24.83	0.60	37.73*	2.10
Gestational Period (weeks)	25.07	1.01	25.90	1.09	25.50	1.31

* p< 0.05 was considered significant on comparison with control SD (Standard Deviation)

Table 2. Comparison of ActivinA and Inhibin A (Biomarkers)

Biomarkers	Group		
	A	B	C
	Mean±SD	Mean±SD	Mean±SD
Activin-A	4.58±1.25	6.35±1.03*	8.74±0.69*#
Inhibin-A	206.70±15.83	207.33±17.33	211.35±19.04

*p< 0.05 was considered significant on comparison with control and with non-obese respectively
SD (Standard Deviation)

Discussion

The study was conducted to evaluate the correlation of biomarkers in pregnancy of gestational diabetic mothers with or without obesity. GDM (gestational diabetes mellitus) can be diagnosed, if fasting plasma glucose level is ≥92mg/dl or post-prandial random blood glucose ≥180mg/dl[13,14]. The World Health Organization (WHO) recommends for using 75-gm sugar for glucose challenge test (GCT) for screening and diagnosis of latent diabetes. The threshold values are a fasting glucose concentration of more than 126 mg/dl (7.0 mmol/l) and/or a 2 hours glucose concentration of more than 140 mg/dl (7.8 mmol/l)[15].

Obesity can be perceived to result in many adverse maternal and neonatal outcomes. Therefore, BMI (body mass index) is considered as the best measure to evaluate obesity and the related health risks. It mainly depends upon the presence of the fat percentage in the body, which could result in insulin resistance, heart problems and increase blood pressure in the long run[16].

After delivery, insulin resistance usually resolves quickly, as far as the need for pharmacological management goes. However, approximately 40-60% of affected women will develop type 2 diabetes mellitus later in their life. They are also at an increased risk of recurrent GDM that presents itself early in any future pregnancies[13].

We found that women with GDM (gestational diabetes mellitus) experienced feeling depression and were upset upon diagnosis, because of the fear of becoming diabetic in the future. This is one of the factors leading to lose of control on blood sugar levels.

The treatment of GDM (gestational diabetes mellitus) are dietary and lifestyle alterations in order to control the increase in weight. The basic management is for the whole duration from pregnancy to lactation, which includes medical treatment, weight management, and physical activity. Women must strictly monitor their fasting and post-meal glucose levels and adjust their individual diet and lifestyle to

meet their glycaemic targets during pregnancy to decrease the risk of any forth coming complications. This approach achieves the glycaemic targets in approximately two-thirds of women with GDM (gestational diabetes mellitus). However, despite the importance of medical nutrition therapy and its widespread recommendation in clinical practice, there are limited data regarding the optimal diet for achieving maternal euglycemia. It is also required to be explored with a number of studies, whether the dietary interventions for achieving maternal glycemia are enough to be effective for reducing excessive foetal growth and adiposity[17].

The secondary outcome of our study is that women with advanced maternal age also tended to have higher BMIs (>25 kg/m^2) than in early age pregnancies. Women with lower BMI than normal, had 28% lower risk of developing the disease while a unit increase in the pre-pregnancy BMI (body mass index), can further increase the likelihood of getting a disease by 0.43% due to the increase in fat portion in the body[18].

Jennifer et al have observed a significant effect on maternal fasting, post-breakfast and post-prandial glucose levels as well as neonatal birth weight outcome by dietary interventions. They need fewer medications but these effects remained inconsistent with other studies[19]. The diet in consideration is the Dietary Approaches to Stop Hypertension (DASH) which is rich in fruits, vegetables, whole grains and low-fat dairy products, and for the low socioeconomic status, there is a low Glycaemic Index (GI) diet which contains green vegetables, most of the fruits, raw carrots, kidney beans, lentils and breakfast cereals. We consider the dietary interventions modified above and beyond usual dietary advice for GDM have the potential to have a better effect on maternal glycaemic control and infant birth weight outcomes. In particular, there is an urgent need for well-designed dietary intervention studies in the lower and middle per-capita income countries where the global health complications of GDM (gestational diabetes mellitus) are more as compare to developed countries where the health facilities are provided up to standard.

A study revealed the significance of early diagnosis of GDM with respect to the gestational weeks as the FPG at 16-20 weeks was quite similar to that of 20-24 weeks, therefore, it can be concluded that early OGTT (oral glucose tolerance test) could help in the prevention from pregnancy related complications later on[20]. These findings coincide with the results identified in a study that states that progression in the gestational weeks enhances the severity of preeclampsia particularly in obese women than the lean ones[22].

The association between BMI and both the biomarkers were found to be significant by raised in the level of activin-A and insignificant to decrease in the level of inhibin-A as depicted in (Table 2). A study revealed that higher concentrations of activin-A in obese individuals as its expression in adipose progenitors increases by the mediators released by macrophages derived from adipose tissues[23]. A study also revealed the presence of higher concentrations of activin-A in adipose tissues, so there is a relation between BMI, that is the fatty proportion of the body and identified it as a potent regulator of human adipocyte progenitor proliferation. It could also mediate fibrosis in obese adipocyte tissues[24]. Gestational diabetes with preeclampsia is generally increasing due to its potential risk factors. In literatures, obesity appeared as a strong, increasing and devastating factor resulting in preeclampsia in diabetic pregnant women[25]. Activin acts to stimulate FSH (follicle stimulating hormone) necessary during pregnancy, contrary to which, inhibin A decreases the level of FSH (follicle stimulating hormone); therefore, a balance between the levels of both protein complexes is significant to keep mother and foetus both, healthy and safe[26].

Therefore, advance research is required to prove the insight that GDM and preeclampsia both have common etiologic pathway. Most of the pregnancy consequences appear to share common conditions for both the diseases, suggesting that they might share same pathophysiology. However, stud-

ies till now didn't contrast relationships between biomarkers and risk factors related to GDM (gestational diabetes mellitus), preeclampsia or both among pregnant women. The studies discussing the mutual and separate pathophysiology of these diseases will provide a better understanding and will encourage researchers and clinicians to line up the screening strategies for the improvement in medications and preventions for GDM and preeclampsia.

The above facts leads us to the basis of identifying the role of activin and inhibin and its contribution in which lead to complications in gestational diabetic pregnant women. The study suggested that activin A and Inhibin A (biomarkers) can be used as a diagnostic tool, which will be helpful in dealing and preventing any future maternal and neonatal complications. The early diagnosis helps in planning pregnancy follow-ups in tertiary health care clinics to provide protection against the adverse perinatal outcomes as well as maternal risks regarding delivery complications.

Conclusion

The study concluded that the disproportionate changes in activin-A and inhibin-A in GDM women is responsible for the increased frequency of pregnancy complications. The excessive increase in activin-A and mild increase in inhibin-A in GDM is responsible for cumulative stimulatory effect of activin A. So, the study revealed that there is a significant increase in activin A in obese and non-obese GDM women and non-significant increase in inhibin-A was observed in obese and non-obese GDM women. The secondary outcome is that there is a significant increase in BMI observed with the increasing age.

Conflict of Interests

Authors have no conflict of interests and received no grant/funding from any organization.

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Answer Picture Quiz: Testicular tumor