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RESEARCH ARTICLE
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EVALUATION OF CITRUS PARADISE FOR CLINICAL EFFECT AND IMPLICATIONS IN WOMEN WITH DIABETES IN PREGNANCY

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ABSTRACT

Objective: Feto-maternal outcomes and Glycemic control in Metformin versus citrus paradise treated Gestational Diabetics

Methodology: This cohort study was conducted from March 2019 to February 2022 at the Department of Obstetrics & Gynecology, Lyari General Hospital Karachi. Pregnant patients presenting in the antenatal clinic at 22-34 weeks of gestation with a singleton pregnancy were subjected to a 75gm oral glucose tolerance test (OGTT). Group 1 was started with Metformin at a dose of 500mg to a maximum dose of 2500mg daily. Group B was given 4 glasses (One glass equal to 250gram) of grapefruit juice daily for pharmacologic effects along with Metformin. Glycosylated hemoglobin (HbA1c), FBS and RBS were measured at the entry to the study and was repeated at each antenatal visit till 36 – 37 weeks of gestation. Maternal and perinatal outcomes were recorded on a predesigned proforma.

Results: In our study, most patients with primigravida 330(66%) and 380(76%) were Group A and B respectively. Fetal outcome mean 7.1±0.78 Apgar score was good in Group-B grapefruit with Metformin as compared with Group-A metformin 7.00±0.79. The mean Weight of the baby was 3±0.23 kg in group A, while 3.1±0.25 kg in group B. When maternal outcomes were tabulated there were significant differences between Group-A and B for HbA1C, FBS and RBS at term, significantly higher in Group-A.

Conclusion: There were lesser neonatal complications and better outcome observed in grapefruits along with metformin group as compared to metformin group in patients with gestational diabetes mellitus.

Keywords: Citrus Paradise, Gestational diabetes mellitus, Metformin

Introduction

Gestational diabetes mellitus (GDM) is known as high blood sugar (glucose) that develops during pregnancy and mostly disappears after giving birth. GDM is a very common medical problem

among pregnant women. It can develop at any stage of pregnancy, but is more common in the second or third trimester. Relative insulin deficiency and its impaired functions leading to maternal hyperglycemia are characteristic features of GDM. It is estimated that 1 in every 7 births are affected by GDM globally[1].Studies as old as 50 years suggest that GDM is a very old medical problem affecting pregnant, although this problem is easily managed and treated with proper diet control and medicine.

In many pregnant women it developed and resolved after delivery of the child, but due to lack of consensus knowledge about levels of hyperglycemia that justify a diagnosis of "gestational diabetes mellitus" (GDM) and treatment during pregnancy made this a huge burden on its incidence globally[2,3]. This results in a large number of maternal, fetal, and neonatal morbidity and mortality. In Pakistan, GDM is a very alarming problem to mother and child health[4].Unfortunately in countries like Pakistan, disease like GDM goes unrecognized with no availability of data on its prevalence and incidence, nor have any preventive strategies developed so far. Although some studies did show some statistics regarding its prevalence ranging from high as 26% in Peshawar, 4.2% and 8% in Karachi<1% in primary gravid females from Lahore, 22% in Balochistan, 14% in Bahawalpur, and 14.8% in Hyderabad[5,6,7] but their authenticity is still questionable.

Metformin, a very known oral hypoglycemic agent, proved to be a very promising strategy for the management of GDM [8]. Many randomized trials are done so far comparing maternal and infant outcomes, and in many of them, metformin has shown to be an effective alternative to insulin and the standard treatment for GDM. But due to the absence of long-term data on the safety of metformin used during pregnancy, concerns regarding potential development effects still remains, which may only be evident later in childhood[9,10].Studies reported that metformin has been shown to cross the placenta, and may affect fetal development in ways that insulin would not. Uncontrolled GDM may increase the risk of childhood overweight/obesity and altered neurodevelopment following neonatal hypoglycemia in infancy[11,12].A Clinical Study presented on defeating diabetes by nutrition showed that grapefruit has a low glycemic index and very low glycemic load and it is the richest citrus fruit rich in antioxidants that make it an ideal choice for managing gestational diabetes[13]. Because of its nutritious value and quality, it also showed positive results in improving insulin resistance and weight management[14]. Thus, grapefruit can be considered effective in managing glucose levels.

Methodology

This cohort-controlled study was conducted from March 2019 to February 2022 at the Department of Obstetrics & Gynecology, Lyari General Hospital Karachi. The study was approved by Ethical Review Committee by Ref# 2018-19/4263 dated 05-01-2019.

Patients with singleton pregnancy, coming to the antenatal clinic at 20-22 weeks of gestation were subjected to a 75gm oral glucose tolerance test (OGTT). International association of pregnancy study group (IADPSG) criteria was followed to diagnose Gestational diabetes mellitus (GDM), patients who have fasting glucose level > 5.1mmol/l (92mg/dl),1 hour≥10 mmol/L (180mg/dl) or 2 hour postprandial glucose level >8.5mmol/l (153mg/dl), were confirmed diagnosed. The pregnant women with other co morbidities, systemic disorder like diabetes mellitus type 1 & type 2, known cases of hypertension& fetal malformation diagnosed on ultrasonography were excluded from the study.

Group A was given 500mg dose of Metformin twice in a day for first week, and the dose was increased to maximum dose of 2500mg in divided doses to achieve glycemic control (fasting blood glucose level < 95mg/dl and 1-hourpostprandial<140mg/dl). Group B was given 4 glasses (One glass equal to 250gram) of grapefruit juice daily for pharmacologic effects[15] along with Metformin.

At every antenatal visit, patients were enquired about sign and symptoms of hypoglycemia. Glycosylated hemoglobin (HbA1c), FBS and RBS were measured at the start of the study of all selected patients, and repeated again at each antenatal visit till 36 – 37 weeks of gestation. The time and mode of delivery were decided according to obstetrical indications. Maternal and perinatal

outcomes were recorded on a predesigned proforma. Data was entered and analyzed using SPSS version 23

Results

A total 1000 patients with GDM were selected in this randomized controlled study. Group-A with 500 patients was given oral Metformin and Group B with 500 patients was given grapefruit juice along with Metformin. Patient demographic characteristics are shown in Table-I. The mean age was 28.56±7.25 years in group A and 29.3±8.00 years in Group B. In our study, most patients with primigravida 330(66%) cases and 380(76%) were Group A and **B** respectively.

Fetal outcome mean 7.8±0.79 Apgar score was good in Group-B grapefruit with Metformin as compared with Group-A Metformin 7.10±0.78. The mean Weight of the baby was **3±0.23**kg in group A, while 3.1±0.25 kg in group B. More babies were healthy and alive in Group B 494(98.8%) as compared with group A 480 (96%), whereas there were 20(4%) and 6(1.2%) intrauterine deaths at term in Group-A and B respectively. When maternal outcomes were tabulated there were significant differences between Groups for HbA1C, FBS and RBS at term, significantly higher in Group-A (Table II).

TABLE I Maternal demographic variables n=1000

Variable	Group-A Metformin N=500	Group-B Grapefruit With Metformin N=500
Age (Years)	28.56±7.25	29.3±8.00
• 15-30 Years	310(62%)	294(58.8%)
• 31-45 Years	190(38%)	206(41.2%)
Parity		
• Primigravida	330(66%)	380(76%)
• Multigravida	170(34%)	120(24%)
Socioeconomic Status		
• Poor Class	405(81%)	415(83%)
• Middle Class	70(14%)	55(11%)
• High Class	25(5%)	30(6%)
Mean Gestational Age Weeks	36.92±1.12	38.43±1.32

Figure I Socioeconomic Status N=100

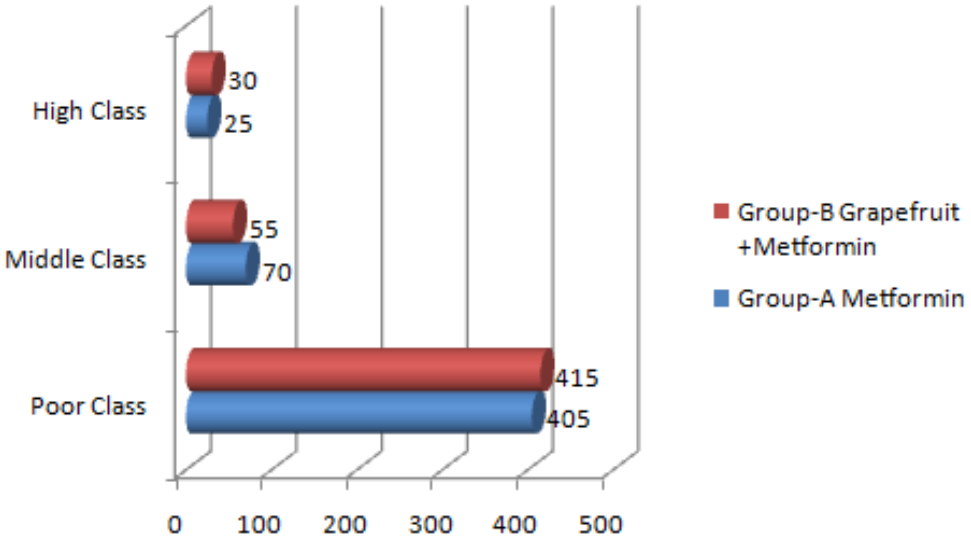
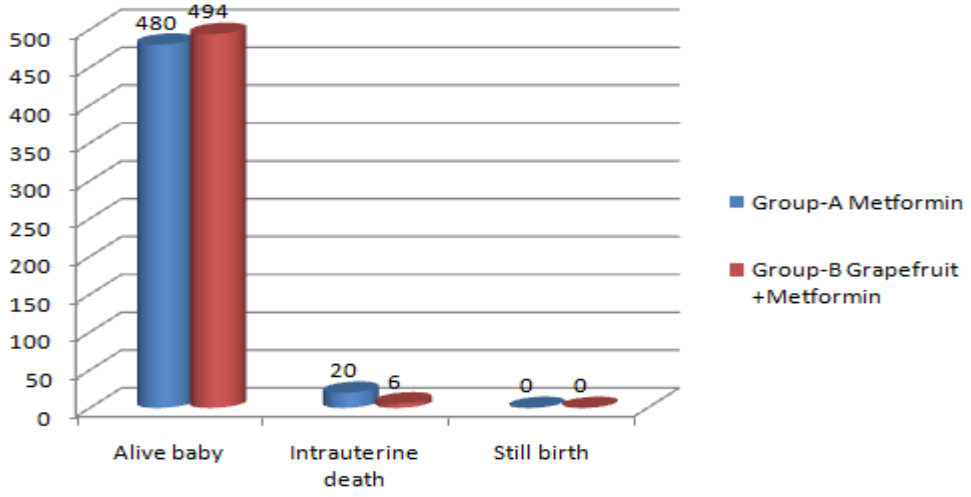


TABLE II Maternal Outcome n=1000

Variable	Group-A Metformin N=500	Group-B Grapefruit With Metformin N=500	P-Value
Mode Of Delivery			
• Vaginal	255(51%)	290(58%)	<0.001
• Assisted Delivery	60(12%)	20(4%)	
• Caesarean	185(37%)	190(38%)	
Fetal Outcomes			
• Apgar Score (Mean)	7.1±0.78	7.80±0.79	0.140
• Mean Weight Of The Baby (Kg)	3±0.23	3.1±0.25	
• Alive Baby	480 (96%)	494(98.8%)	
• Intrauterine Death	20 (4%)	6(1.2%)	
• Still Birth	0	0	
Maternal Outcomes			
• Hba1c(36weeks)	4.9±1.91	4.6±0.45	<0.001
• Fbs (36weeks)	90.45±2.11	81±7.16	<0.001
• Rbs (36weeks)	185.5±4.21	163.25±2.11	0.003

Figure II Fetal Outcomes N=1000



Discussion:

Diabetes mellitus is a syndrome of great importance, the number of cases is increasing drastically every day. In particular, diabetes is a common and important disease during pregnancy causing fatal complications, in both fetus and the mother. It increases the risks of morbidity and mortality for diabetic pregnant women and their offspring[16]. Hypoglycemic drugs such as, metformin or insulin are given to treat diabetes, but regular exercise and an adequate diet have also been indicated. Most people use coadjutant therapies to treat diabetes-induced hyperglycemia, either within or outside the context of pregnancy, such as medicinal plants, herbs, and fruits are popularly used among people with hyperglycemia[16,17]. However, studies examining grapefruit usage for diabetes treatment are necessary to confirm their possible effects and safety for the mother and fetus.Our study observed GDM is generally more prevalent in between 20 to 30 years of age of patients were 28.56±7.25 and 29.3±8.00 years in groups. However, the study of Tayyiba Wasim reported the means of GDM were 29.5±4.8 years in metformin and 29.7±4.8 years in the insulin group[18].

Flavonoids are bioactive compounds and are reported to help reduce the risk of developing cardiovascular diseases and diabetes[19]. Citrus fruits are a rich source of (poly) phenolic flavonoids, mainly flavanones, including hesperidin, naringin, narirutin, and neohesperidin (approximately 90% of total flavonoids)[19], together with the poly methoxy flavones, tangeretin and nobiletin[20]. Citrus fruits are widely consumed worldwide, both in fresh and processed forms. The well-known, widely consumed fruits within this genus are oranges, mandarins, tangerines, grapefruit, lime, and lemons,

with oranges being more than 50% of total citrus produced and consumed each year[21].We found grapefruit along with metformin to be significantly more effective in achieving glycemic control at 36/37 weeks as compared to the metformin group. Fasting blood glucose levels were significantly better controlled at the time of delivery in patients who were taking grapefruit along with metformin, although HBA1c levels were comparable. Grapefruit along with metformin being an oral drug contributes a lot to achieving promising results with better acceptance and compliance[22,23]. Our studies showed positive results of glycemic control in patients taking grapefruit along with metformin.

Along with good maternal glycemic control, our study results also showed good neonatal outcomes with the use of grapefruit along with metformin as compared with metformin. At the same time, the results of studies on the long-term impact of grapefruit along with metformin use are very encouraging. Neonates whose mothers received grapefruit along with metformin during pregnancy are born with normal weight and Apgar score.

GDM have many complications, which can lead to fatal outcome, macrosomia and neonatal hypoglycemia are the commonest complications found in babies of GDM mothers. These conditions can be prevented by controlled Diabetes. In our study, glycemic control was better in patients taking grapefruit along with metformin. As metformin crosses the placenta and it has a direct effect on fetal physiology leads to a better neonatal profile including less hypoglycemia and decreased macrosomia. The majority of RCTs have shown similar results with a lesser incidence of neonatal morbidity in patients taking metformin [24,25].

Our study reports 20(4%) perinatal deaths in the metformin group-A at 36 weeks and 6(1.2%) neonatal deaths in the grapefruit along with metformin group-B. All these mothers had poor glycemic control during pregnancy thereby emphasizing the importance of good glycemic control during pregnancy.

Conclusion

With the use of grapefruit along with metformin in pregnancy, better glycemic control of GDM mothers is seen, and better neonatal outcomes are achieved. The grapefruit along with metformin is well responded in patients with good compliance. Neonatal complications drastically decreased, with grapefruit along with metformin use as compared to metformin only in patients with gestational diabetes mellitus.

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