Comparative Study between Metformine and Vitamine "D" In Management of Insulin Resistance in Type II Gestational Diabetes

Madiha M. Hanafy, Lamyaa M. Yousry, Rania F. Okasha

Obstetrics and Gynecology Department, Faculty of Medicine (for Girls) Al Azhar University
Rania_wasef@yahoo.com

Abstract: Background: Traditionally, insulin has been the gold standard in the management of Type 2 gestational diabetes. However, insulin therapy can be inconvenient, This has led to the exploration of oral hypoglycemic agents as an alternative to insulin therapy, the use of insulin sensitizing agents like metformin and vitamin D in pregnant women is still controversial, therefore, this study aims to examine the efficiency and safety of metformin and vitamin D and comparing the effects of these drug son maternal and neonatal outcomes in gestational diabetes mellitus. **Methods**: Setting: Alzahraa university hospital This is prospective intervention clinical study, including 60 pregnant women with type II diabetes mellitus in the period between January 2016 to January 2018. Patients were divided into 3 groups Group A**:** who was prescribed vitamin D therapy**.** Group B: who was prescribed metformin therapy, Group C**:** who was prescribed insulin therapy after failure of vitamin D or metformin. **Results**: This study detected that there is good control of blood surgar in group A, this was shown in the form of improvement in fasting blood glucose, in post prandial blood glucose level, fasting serum insulin (FI), HbA1C and fasting glucose/insulin ratio (G/I) with p-value <0.001. Also good control of blood surgars in group B, this shown in the form of improvement in fasting sugars, in post prandial blood sugars level, HbA1C and G/I ratio with p-value <0.001. **Conclusion**: Metformin and vitamin D supplementations are effective in management of pregnant women with type II GDM and should be recommended in management of gestational diabetes prior to insulin.

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Keywords: Comparative; Study; Metformine; Vitamine; Insulin Resistance; Gestational Diabetes

1. Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance of variable severity with onset of first recognition during pregnancy **(1).**

Hyperglycaemia during pregnancy is found to be associated with various maternal and perinatal adverse outcomes (**2).** Their offsprings will have a life-long increase risk of glucose intolerance, obesity and metabolic syndrome whereas the mothers will have a higher risk of metabolic syndrome and diabetes in the future **(3).**

Pregnancy is an insulin-resistant state during which improved B-cell function and proliferation normally occur to meet increased secretory demands **(4).** The initial treatment in these patients with Type 2 diabetes gestational diabetes is by diet modification and in the event of failure of control with diet, treatment is shifted to insulin to achieve tight glucose control with no risk of placental transfer **(5).** However, insulin therapy can be inconvenient because of the need for multiple injections, its associated cost, pain at injection site, need for refrigeration, and skillful handling (a problem in low resource countries), and all these has contributed to poor patient compliance. This has also led to the search for oral hypoglycemic agents as an alternative option to insulin therapy **(6).** Oral metformin is a logical option for women with gestational diabetes mellitus. It improves insulin sensitivity, probably by activating AMP kinase, and is not associated with weight gain or hypoglycemia **(7).**

There is emerging evidence about the safety and efficacy of metformin, a licensed first line therapy for the treatment of type II diabetes in pregnancy **(8).** Also there is an evidence suggests that vitamin D contributes to insulin sensitivity, or B-cell function and insulin secretion and its deficiency may contribute to impaired glucose tolerance during pregnancy **(4).**

Aim of the study

Evaluation of the role of insulin sensitizing agents (Metformin & vitamin D) on glucose tolerance of type II gestational diabetic patients.

2. Methods

Study Selection: a retrospective study was conducted on patients with type II gestational diabetes to compare the effect of metformin and vitamin D on maternal outcome and neonatal outcomes.

Data Extraction and Quality Assessment: We extracted following information from our study. Maternal outcomes contain glycemic control, incidence of cesarean section and vaginal delivery,

preterm delivery (delivery before 37 wk). Neonatal outcomes include birthweight, neonatal intensive care unit (NICU) admission.

Statistical Analysis: Statistical analysis was done using one-way ANOVA if its assumptions were fulfilled, otherwise Kruskal-Wallis test was used to compare between 2 groups unpaired T-test was used. Tukey's HSD test or Mann-Whitney test were used as post hoc tests whenever indicated. Between-groups comparisons of categorical variables were performed by Chi-square test (x2). Any difference with p value < 0.05 was considered statistically significant. Any difference with p value < 0.001 was considered statistically highly significant. Any difference with p value > 0.05 was considered statistically non-significant.

3. Results

Study Characteristics

The study shows no significant differences between the two groups regarding gestational age and BMI as shown in table (1).

Main Maternal Outcomes

Glycemic control.

Table (1): Show the gestational age and BMI as two of the clinical characteristics of participants of the different groups

		Vit. D (Group A)	Metformin (Group B)	Insulin (Group C)	Test value	P-value	P1	P2	P3
		No.= 20	No.= 20	No.= 20					
BMI	Mean ± SD	24.83 ± 3.23	26.87 ± 4.44	26.26 ± 3.46	1.542•	0.223	0.089	0.263	0.619
	Range	18.5 – 32	19.5 – 35	19.5 – 32					
GA	Mean ± SD	26.58 ± 1.46	26.26 ± 1.51	26.71 ± 1.45	0.491•	0.615	0.491	0.798	0.351
	Range	23 – 28	24 – 28	24 – 28					

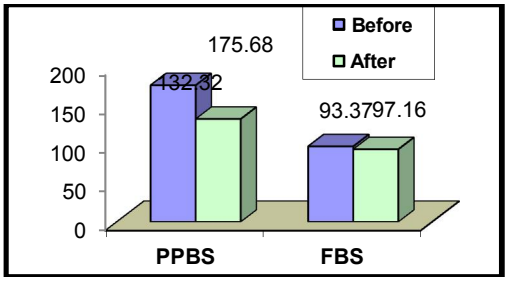

Figure (1) Comparsion of the pre and post treatment FBS and PPBS in (Group A)

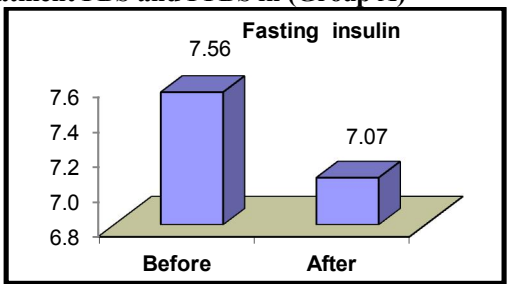

Figure (2) Comparsion of the pre and post treatment Fasting insulin in (Group A)

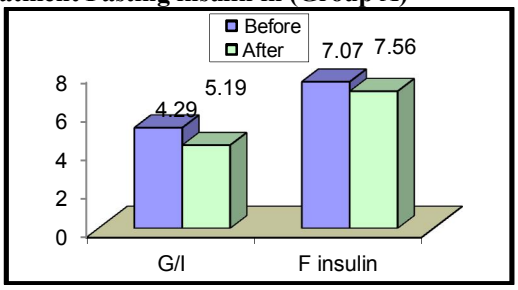

Figure (3) Comparsion of the pre and post treatment G/I and HbA1C in (Group A)

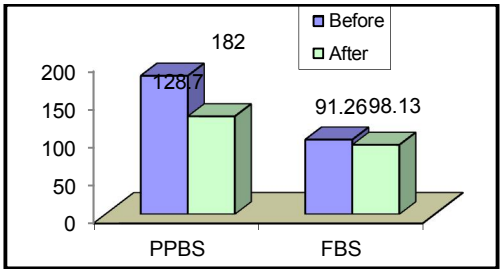

Figure (4) Comparsion of the pre and post treatment FBS and PPBS in (Group B)

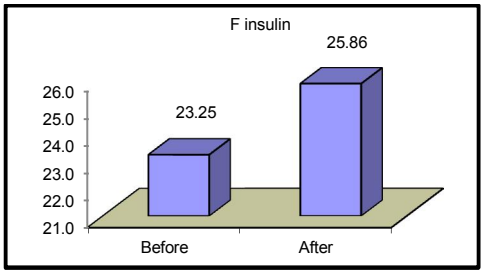

Figure (5) Comparsion of the pre and post treatment Fasting insulin in (Group B)

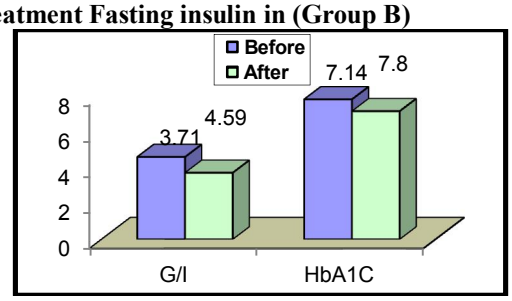

Figure (6) Comparsion of the pre and post treatment G/I and HbA1C in (Group B)

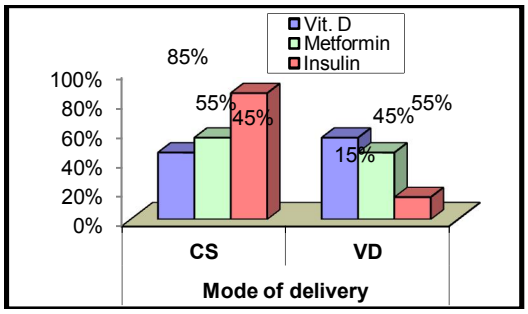

Figure (7) Comparison of mode of delivery in the different groups of the study

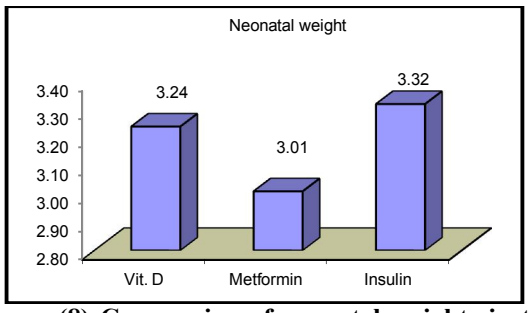

Figure (8) Comparsion of neonatal weights in the different groups of the study.

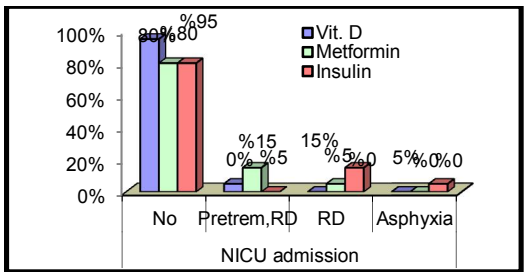

Figure (9) NICU admission for the different groups of the study and causes of NICU admission.

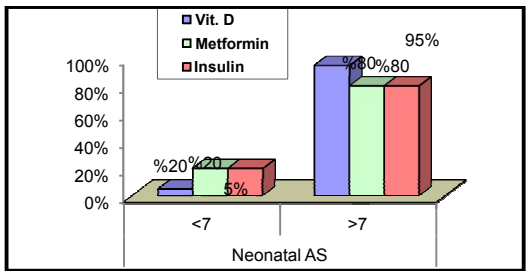

Figure (10) Neonatal Apgar score in the differentgroups of the study

The current study shows good control of blood surgar in group A, this shown in the form of improvement in fasting blood sugar from (mean 97.16 ± 4.89) to (mean 93.37 ± 3.29), in post prandial blood sugars level from ((mean 175.68± 27.28) to (mean 132.32 ± 32.89) with with p-value <0.001,, fasting serum insulin (22.68 ± 7.91) to (24.42 ± 7.45) with p-value <0.001, HbA1C from (7.56 ± 0.91) to (7.07 ± 0.60) with p-value <0.001 and G/I ratio from (5.19 ± 2.83) to (4.29 ± 1.80) with p-value <0.001(as shown in figures 1,2,3) Also good control of blood surgar in group B, this was shown in the form of improvement in fasting sugars from (98.13 ± 5.82) to (91.26 ± 3.56), in post prandial blood sugars level from (182.00 ± 13.87) to (128.70 ± 8.08) with with p-value <0.001, FI from (23.25 ± 5.97) to (25.86 ± 5.77) with p-value <0.001, HbA1C from (7.80 ± 0.56) to (7.14 ± 0.40) with p-value <0.001 and G/I ratio from 4.59 ± 1.62) to (3.71 ± 1.18) with p-value <0.001. **(as shown in figures 4,5,6).**

Mode of delivery: There was significant increase in rate of delivery by cesarean section in the different groups of the study (45%) in Group A, (55%) in Group B, with more increase in Group C (85%). as shown in figure 7.

Main neonatal outcome: There was no significant difference in neonatal weight (wt) in the different groups of the study, in Group A neonatal wt ranged from 2.1-4.1 with (mean 3.24± 0.45), in Group B, neonatal wt ranged from 1.2-3.9 with (mean 3.01± 0.62), in Group C, neonatal wt ranged from2.4 -4.8 with (mean 3.32 ± 0.0.59),, p-value (0.201). the most increase in neonatal wt was in Group C, as sown in figure 8.

There was no significancant difference in neonatal intensive care unit (NICU) admission, with P value (0.154) in the different groups of the study, in Group A 5% needed NICU admission, in Group B 20% needed NICU admission, in Group C 20% needed NICU admission, the most common cause for NICU admission in the different Groups of the study was prematurity and respiratory distress, with preterm delivery more in Group B (15%), as shown in figure 9.

There was no significance difference in APGAR score (AS) in the different groups of the study with P value (0.151), in Group A 95%, with AS >7, in Group B 80% with AS >7, in Group C 80% AS >7, As shown in Figure 10.

4. Discussion

In the current study there was good control of blood surgar in group A, This result is in agree with a study involved 12 women with GDM who had sequential oral glucose tolerance test (OGTTs) before and 2h after administration of

vitamin D3, Treatment resulted in increase in serum vitamin D levels and fall in fasting and post prandial serum glucose levels **(9).**

Also our study is in agree with a more recently, double-blinded randomized controlled trial in 54 women diagnosed with GDM reported an improvement in fasting and postprandial blood

glucose level after adminstation of vitamin D given 21 days apart compared with placebo **(10).**

Evidences showed that vitamin D metabolism is related to diabetes incidence and its exacerbations. In most studies on pancreas *in vitro* or *in vivo*, results have shown that there are vitamin D receptors and vitamin D_3 binding proteins in pancreatic beta cells and in this way vitamin D can be influential in insulin secretion. Moreover, in studies on rats, vitamin D deficiency is associated with lower insulin secretion, and vitamin D supplementation therapy caused appropriate insulin secretion and improved glucose tolerance in these animals **(11).**

Another study was conducted from September 2013-November 2013 on 56 pregnant women between the ages of 18-40 with GDM. Twenty eight women received 50,000 units of vitamin D_3, while the other twenty eight were assigned to placebo pills, The women who received vitamin D supplementations had a significant reduction in fasting plasma glucose compared to the placebo (−0.89±0.69 vs +0.26±0.92 mmol/L; P <.001). In addition, there was also a significant reduction in serum low density lipoprotein (LDL), total cholesterol and a significant elevation in high density lipoprotein (HDL) levels compared with women who received placebo. Women who had GDM benefitted from taking supplemental vitamin D, These supplements of vitamin D are important to the patient's metabolic profile because it has potentials to avoid long-term maternal and perinatal complications (*12).*

In the current study there is good control of blood surgar in group B, this shown in the form of improvement in **fasting sugar** from (98.13 ± 5.82) to (91.26 ± 3.56), in **post prandial blood** sugars level from (182.00 ± 13.87) to (128.70 ± 8.08) with with p-value <0.001, **FI** from **(**23.25 ± 5.97) to (25.86 ± 5.77) with p-value <0.001**, HbA1C** from (7.80 ± 0.56) to (7.14 ± 0.40) with p-value <0.001 and **G/I** ratio from 4.59 ± 1.62) to (3.71 ± 1.18) with p-value <0.001**.**

This is in agree with randomized trials, using metformin during GDM, showed favorable results of metformin in GDM appearing in significant reduction in both fasting and postprandaial blood sugar **(13).**

A study done by **Moore, et al., 2007** showed that, metformin dose of 500 mg twice daily was found to be equivalent to insulin, in achieving glycemic control in 84% of cases **(14)**. In the current study, There was no significancant difference in APGAR score and neonatal outcome in the different groups of the study with P value (0.151), in Group A 95%, with AS >7, in Group B 80% with AS >7, in Group C 80% AS >7. This is in agree with randomized trials, using metformin during GDM, showed favorable results of metformin in GDM and finds no difference in any neonatal outcome compared to insulin **(13).**

In the current study, There was significant difference between group B and group C according to control of fasting and postprandial blood glucose levels, with better glycemic control in group C (insulin group) compared to group B (Metformin group) with p-value (<0.001).

This is in contrast with two observational studies by **Rai et al.,2009** and **Goh et al.,2011** they suggested better glucose control in the metformin arm compared to insulin, this difference may be attributed that the current study design, as insulin group in the current study started insulin only after failure of metformin or vitamin D **(15), (16).**

In the current study, There was no significant difference in NICU admission and neonatal outcome, with P value (0.154) in the different groups of the study, in Group A 5%, needed NICU admission, in Group B 20% needed NICU admission, in Group C 20% needed NICU admission.

This is in contrast with an observational study by **Hellmuth et al., 2000** which was conducted in population of GDM, hinted at significantly higher perinatal mortality (P < 0.02) in metformin treated mothers **(17).** This difference may be attributed to less number of patients in the current study.

In the current study, the most common cause for NICU dmission in the different Groups was prematurity and respiratory distress, with incidence of preterm delivery was more in Group B (15%).

This is in agree with a study done by **Rowan JA, et al.,2008** which suggested that, no significant increase in composite measures of neonatal complications in metformin treated mother. However, the frequency of preterm birth (before 37 gestational weeks), was higher in the metformin group compared to insulin group (P = 0.04). **(8).**

It was observed that the increase in preterm birth was related to greater frequency of spontaneous causes, rather than iatrogenic, and it was not associated with a higher rate of any neonatal complications. This might also suggest that preterm birth could have happened either due to chance or to an unrecognized effect of metformin on labor process **(8)**.

Furthermore, the current study in contrast with, one study by **Goh et al.,2011** hinted at significantly lesser preterm birth in metformin treated mothers (12.5% vs. 19.2% in insulin; P = 0.005). this may be attributed to less number of cases in the current study **(16).**

Also in the current study there was no significant difference in neonatal weight in the different groups of the study, in Group A neonatal wt ranged from 2.1-4.1 with (mean 3.24± 0.45), in Group B, neonatal wt ranged from 1.2-3.9 with (mean 3.01± 0.62), in Group C, neonatal wt ranged from 2.4 -4.8 with (mean 3.32 ±

0.0.59), p-value (0.201). This is in contrast with a study by **Hasan et al.,2012** who found that Macrosomia was significantly lesser in metformin treated mother (10.65% vs. 18.67% in the insulin group, P < 0.05). This may be attributed to proper antenatal care and good control of diabetes in patients of the current study, resulting in less complications of diabetes including macrosomia. **(18)**

Conclusions:

Metformin and vitamin D supplementations are effective in management of pregnant women with type II GDM and should be recommended in management of gestational diabetes prior to insulin.

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