Original Article

COMPARISON OF DETEMIR VERSUS NEUTRAL PROTAMINE HAGEDORN FOR MANAGEMENT OF FEMALES PRESENTING WITH DIABETES DURING PREGNANCY.

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is the type of diabetes, first diagnosed during pregnancy. Increased Body mass index (BMI), previous history of gestational diabetes, family history of type II diabetes and polycystic ovarian syndrome are risk factors for the development of gestational diabetes mellitus. Gestational diabetes resolves after pregnancy in most cases. The main objective of the study was to compare the efficacy with Detemir versus Neutral Protamine Hagedorn for management of pregnant females presenting with gestational diabetes.

Material and Methods: A randomized Control Trial was carried out in obstetrics & gynecology department, Unit I, Services Hospital, Lahore for 6 months from 05-04-2018 to 05-10-2018. Total of 710 females were inducted into study. Then participants of study were divided into two groups. Then females were advised to take one shot daily at same time and followed-up till 36 weeks. Reports were assessed and level of HbA1c was noted. If HbA1c<6.0%, the efficacy labeled. SPSS version 20 was used to analyze all the collected data.

Results: The mean age of participants in Detemir group was 29.25±6.14 years whereas in the NPH group was 29.97±5.97 years. Efficacy was achieved in 267 cases (175 with determine vs. 92 with NPH, p-value=0.001).

Conclusion: Detemir is significantly more effective than NPH for management of pregnant females presenting with gestational diabetes.

Key Words: Gestational diabetes mellitus, Blood glucose level, Body mass index

INTRODUCTION

Gestational diabetes mellitus (GDM) is the type of diabetes, first diagnosed during pregnancy. International Association of Diabetes in Pregnancy Study Groups (IADPSG) recommended criteria are followed in diagnosing GDM and this is based on Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study.

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Implications of GDM are both on fetus and mother and early diagnosis and treatment of GDM should be done to improve pregnancy outcome.[1]

Pregnancy exerts a diabetogenic effect, even in women not having diabetes, and so it affects feto maternal metabolism. The reported incidence of GDM is 2% to 14% among pregnant females. The first line of therapy for women diagnosed with gestational diabetes is lifestyle and diet modification; and when these changes fail to bring required glycemic control, drugs like insulin should be added.[2]

Healthcare providers must have a proper understanding of managing gestational diabetes with insulin, to give absolute care to pregnant women diagnosed with diabetes.[3] Unfortunately, to achieve euglycemia, the available preparations of insulin and treatment regimens are not sufficient.[4] Randomized controlled trials studying basal

insulin analogs for the treatment of gestational diabetic women are sparse.[5]

Detemir is as good as Neutral Protamine Hagedorn (NPH) in terms of perinatal outcomes in women whose pregnancy has been complicated with gestational diabetes and so far, no safety concerns have been reported.[6] A randomized trial conducted in 2012 found that with Detemir, the efficacy (HbA1c<6.0% at 36 weeks) was achieved in 41% cases while with NPH in 32% cases. The difference, however, was insignificant (p=0.280).[7]

The rationale to conduct this study was to compare the efficacy of Detemir versus NPH for management of pregnant females presenting with gestational diabetes. Literature has reported that Detemir is more effective than NPH without compromising the health of pregnant female and also cause fewer side effects like hypoglycemia. But the work done in this regard is not sufficient and local data is lacking altogether. So we want to conduct this study to find the more effective drug. To enable the results of this study to be implemented in the future.

MATERIAL AND METHODS

A randomized Control Trial was carried out in obstetrics & gynecology department, Unit II, Services Hospital, Lahore for 6 months from 05-04-2018 to 05-10-2018. In total, 710 participants were enrolled in trial by using non-probability, consecutive sampling. The calculated sample size was 710 cases; 355 in both groups with power of test as 80%, level of significance as 5% and taking percentage of efficacy i.e. 41% with Detemir and 32% with NPH in pregnant females presenting with GDM. Pregnant females ranging from 18-40 years of age presenting during gestational age >20 weeks (on USG) presenting with GDM (as per operational definition) were included in study. Patients having pregnancy complicated with hypertensive disorder and those already diagnosed as a case of type 1 or type 2 diabetes were not included in this study.

Prior approval was taken from ethical committee of the Hospital (IRB). The 710 females who fulfilled the selection criteria were included in study. Informed consent was gained. Demographic information (age, name, parity, gestational age, and contact) was also obtained. Then participants were randomly grouped in two by using lottery method. Females in group 1 were given subcutaneous Detemir (100 units/mL; Novo Nordisk) while in group 2, females were given subcutaneous NPH (100 units/mL; Novo Nordisk). Then females were advised to take one shot daily at same time and were followed-up till 36 weeks. At 36 weeks of pregnancy, blood sample of the female was taken and was sent to the pathology department of hospital for measurement of HbA1c. Level of HbA1c was noted. If HbA1c<6.0%, the efficacy was labeled (as per operational definition). A pre-designed proforma was used to collect all the information. SPSS version 20 was used to analyze all the collected data. Quantitative variables like age, gestational age, HbA1c were calculated as mean and standard deviation. Qualitative variables like parity and efficacy were calculated as frequency and percentage. To compare both groups, the Chi-Square test was taken into use. The significant value of the chi-square test was set as P-value ≤0.05. Data stratification for age, BMI and parity was done. Chi-square test was applied to compare the efficacy in stratified groups taking p-value≤0.05 as significant.

RESULTS

In this study total of 710 females were enrolled. The mean age of the females in the Detemir group was 29.25±6.14 years whereas it was 29.97±5.97 years in the NPH group. The mean gestational age of the females in Detemir group was 26.29±3.73 weeks whereas in NPH group it was 25.54±3.69 weeks. The mean value of BMI of the females in Detemir group was 25.58± 4.07 kg/m2 whereas the mean value of BMI in NPH group was 25.59±4.062 kg/m2. The mean value of HbA1c at 36 weeks of the females in Detemir group was 6.21± 1.47 whereas the mean value of HbA1c of the

females in NPH group was 7.42±1.62. (Table-1)

Table-1: Comparison of age, gestational age, BMI and HbA1c at 36 weeks in study groups

		Group Study	
		Detemir	NPH
Age (years)	N	355	355
	Means	29.25	29.97
	SD	6.14	5.97
Gestational age (weeks)	N	355	355
	Means	26.29	25.54
	SD	3.73	3.69
BMI (Kg/m2)	N	355	355
	Means	25.58	25.59
	SD	4.07	4.062
HbA1c 36 weeks	N	355	355
	Means	6.21	7.42
	SD	1.47	1.62

In the present study, there were 144(20.28%) nulliparous females, 158(22.25%) had parity 1, 135(19.01%) females had parity 2, 120(16.90%) females had parity 3, 75(10.56%) females had parity 4 and 78(10.99%) females had parity 5. (Figure-1)

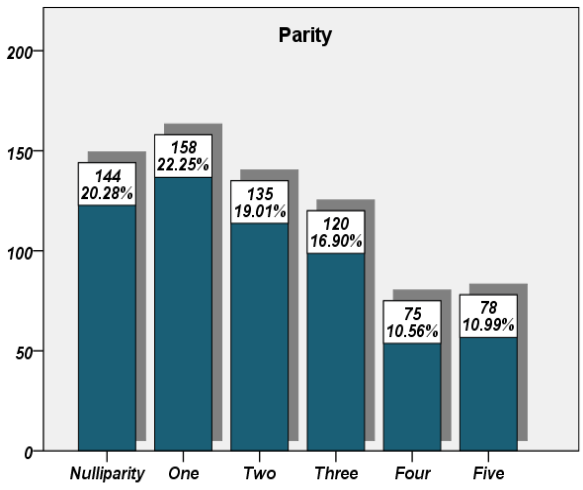

Figure-1: Frequency distribution of parity

According to this study, 267 females achieved efficacy, in which 175 were from Detemir group and 92 were from NPH group. Similarly, 443 females did not achieve efficacy, in which 180 belonged to Detemir group and 263 belonged to NPH group. Between study groups, significant statistical difference was found with efficacy i.e. p-value=0.001. (Table-2)

Table-2: Comparison of efficacy in study groups

		Group Study		
		Detemir	NPH	Total
Efficacy	Yes	175	92	**267**
	No	180	263	**443**
Total		**355**	**355**	**710**

Chi value=41.35
p-value=0.001*

The results of this study clearly showed that among females with age ≤ 30 years, 160 females achieved efficacy of which 103 belonged to Detemir group and 57 belonged to NPH group. Likewise the females with age > 30 years, 107 females achieved efficacy of which 72 belonged to Detemir group and 35 belonged to NPH group. Between study groups, significant statistical difference was found with efficacy stratified by age i.e. p-value=0.001 & 0.001 respectively. (Table-3)

Table-3: Comparison of efficacy in study groups stratified by age

Age (years)	Efficacy	Study Groups		Total	p-value
		Dete-mir	NPH		
≤ 30	Yes	103	57	**160**	**0.001**
	No	103	126	**229**	
> 30	Yes	72	35	**107**	**0.001**
	No	77	137	**214**	

The study results showed that among females of primary parity, 124 females achieved efficacy, of which 78 belonged to Detemir group and 46 belonged to NPH group. Likewise, the females with multiparity, 143 females achieved efficacy, of which 97 belonged to Detemir group and 46 belonged to NPH group. Between study groups, significant statistical difference was found with efficacy stratified by parity i.e. p-value=0.002 & 0.001 respectively. (Table-4)

Table-4: Comparison of efficacy in study groups stratified by parity

Age (years)	Efficacy	Study Groups		Total	p-value
		Dete-mir	NPH		
Primary	**Yes**	78	45	**124**	**0.002**
	No	79	99	178	
Multiple	**Yes**	97	46	143	**0.001**
	No	101	164	265	

The study results showed that among females with normal BMI, 119 females achieved efficacy of which 81 belonged to Detemir group and 38 belonged to NPH group. Likewise, the females with abnormal BMI, 148 females achieved efficacy of which 94 belonged to Detemir group and 54 belonged to NPH group. Between study groups, significant statistical difference was found with efficacy stratified by BMI i.e. p-value=0.001 & 0.001 respectively. (Table-5)

Table-5: Comparison of efficacy in study groups stratified by BMI

Age (years)	Efficacy	Study Groups		Total	p-value
		Dete-mir	NPH		
Normal	**Yes**	81	38	119	0.001
	No	84	127	211	
Abnormal	**Yes**	94	54	148	0.001
	No	96	136	232	

DISCUSSION

GDM develops during pregnancy. It means that a woman was having a normal blood glucose level before pregnancy now has raised blood glucose levels in pregnancy. During pregnancy, a balance is maintained between placental hormones, which increase blood glucose level, and pancreatic insulin. In GDM, this balance is disturbed by increase hormonal production by the placenta and blood glucose levels are increased

In this study the efficacy regarding the management of pregnant females presenting with GDM was achieved in 267 females in which 175 were from Detemir group 92 were from NPH group. Between study groups, significant statistical difference was found with efficacy i.e. p-value=0.001.

A study by Russell-Jones D et al. concluded that once-daily dosage of insulin Detemir at bedtime, provided better fasting blood glucose level with persistence in daily levels and steady control of mean blood glucose level over 24 hours as compared to NPH insulin, also, to decrease risk of night time hypoglycemia.[8] If the insulin Detemir is administered in evening time, it can further improve the fasting blood glucose levels, as findings suggest in study.[9]

Detemir is as good as Neutral Protamine Hagedorn (NPH) in terms of perinatal outcomes in women whose pregnancy has been complicated with gestational diabetes and so far, no safety concerns have been reported.[6]

Pollock RF and Chubb B concluded that the short-term evaluation of health economics revealed that insulin Detemir is an alternative to insulin NPH in the United Kingdom as it has lower rates of hypoglycemia in Type 1 and Type 2 Diabetes and fewer chances of weight gain in Type 2 Diabetes.[10]

One study demonstrated that the Detemir insulin is a convenient substitute for NPH insulin in terms of cost in insulin naive type 2 Diabetics patients.[11]

One more study by B. M. Frier et al concluded that insulin Detemir treatment provided better outcomes in terms of better glycemic controls, decreased day to day variability of blood glucose, lower incidence of hypoglycemia and less weight gain as compared with NPH insulin.[12] Another study concluded that Detemir insulin is associated with significantly good control of fasting blood glucose levels, and almost same control of HbA1C and incidence of hypoglycemia compared with NPH.[13] On the other hand, study showed NPH and Detemir to have almost the same efficacy in term of mean blood glucose control.[14]

One more study by Kimberly M. Herrera et al also resulted that Detemir insulin is as effective as NPH Insulin for the management of GDM and Type 2 Diabetes in pregnancy.

[15] No significant difference was found in both groups in terms of weight gain & perinatal outcome. The NPH group reported more incidence of hypoglycemia per participant.
A randomized trial conducted in 2012 found that with Detemir, the efficacy (HbA1c<6.0% at 36 weeks) was achieved in 41% cases while with NPH in 32% cases. However, the difference was insignificant (p=0.280).[7]

CONCLUSION

This study concluded that the Insulin Detemir is significantly more effective than insulin NPH for management of pregnant females presenting with GDM.

AUTHOR'S CONTRIBUTION

MK: Data collection
MR: Study design
KK: Conception of idea
MU: Drafting article
HN: Editing
NA: Data analysis

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