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**Original Article**

# The Efficacy of Insulin Detemir Versus Neutral Protamine Hagedorn Insulin in Treatment of Gestational Diabetes Mellitus During Pregnancy

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## Abstract

**Background:** The gestational diabetes mellitus (GDM) is one of the most common medical conditions during pregnancy. Insulin is considered to be safe in pregnancy. As compared to Neutral Protamine Hagedorn Insulin (NPH)" insulin detemir shows good safety and efficacy for future use in GDM for better cure.
**Objectives:** To compare the outcome of insulin detemir plus Novolin R versus NPH plus Novolin R in women with GDM.
**Methods:** This experimental study was conducted in outpatient Department of Obstetrics & Gynae., Unit I, Services Hospital, Lahore from February 2021 to February 2022. After taking ethical approval and informed consent, patients were selected by probability double blind sampling technique and randomized in two groups. In group A, patient received insulin detemir plus Novolin R. In group B, patients received insulin NPH plus Novolin R. At baseline and after 3 weeks of treatment, fasting and post-prandial sugar levels were measured and compared for mean change in blood sugar level.
**Results:** In detemir group, the mean fasting blood sugar level was 156.74±16.80 g/dl, which was reduced to 99.34±16.82 g/dl after treatment. In NPH group, the mean fasting blood sugar level was 155.01±18.81 g/dl, and reduced to 104.70±18.97 g/dl after treatment with significant ($p$ <0.05). In detemir group, the mean post-prandial sugar level was 222.44±37.88 g/dl, and reduced to 142.00±15.74 g/dl after treatment. In NPH group, the mean post-prandial sugar level was 210.90±38.39 g/dl, and reduced to 147.97±7.05 g/dl after treatment and the reduction was significant ($p$-value <0.05).
**Conclusion:** The detemir was found to be more effective in controlling blood sugar level than NPH in pregnancy.
**Key words:** Insulin, gestational diabetes, outcome, comparison.

## Introduction

Gestational diabetes mellitus (GDM) is the metabolic disorder with intolerance of glucose level in blood. It can be identified in third trimester of pregnancy. It may be due to an abnormal placental-vascular functions. GDM-associated hyperglycemia affects the placenta with improper growth and functions.[1] Due to the changing lifestyles and dietary patterns, the rising rate of obesity is closely correlated with it.[2] Worldwide prevalence of GDM is 1-14%,while in Pakistan it is around 16.7%. Maternal hyperglycemia is associated with short and long term adverse fetomaternal outcomes. In developing countries with compromised healthcare system, the GDM is serious threat to both mother and fetus.[3] The poor glycemic control, is linked to a higher risk of adverse pregnancy outcomes like congenital anomalies, ploy hydramnios and macrosomia. The first line of treatment is extensive lifestyle adjustment, which frequently necessitates behavioral and dietary changes to achieve optimal glycemic control.[4]

The management of GDM involves multidisciplinary approach, health education plays significant role regarding proper management.[5] Most women have poor concept of GDM

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RB & AM conceptualized the project and did the literature search. AM & SS did the data collection. RB, DR & HR performed the statistical analysis. Drafting, revision & writing of manuscript were done by AT & & AH.

complications. In multidisciplinary approach, the role of health education is fundamental. The treatment of GDM starts with non-pharmacological measures like diet control and exercise and usually oral metformin and insulin therapy is recommended as gold standard when the targeted glycemic control is not achieved. Insulin is considered to be safe in pregnancy. The safety profile of other medications like metformin during pregnancy is still under debate.[6] Various insulin preparations are available in market. Insulin secretion during and after meals should be considered in mind while prescribing insulin analogues.

The rationale of the study was to compare the outcome of insulin detemir plus Novolin R versus NPH plus Novolin R in women with GDM in Pakistani Population

## Methods

The Descriptive observational study was conducted in outpatient Department of Obstetrics & Gynaecology Unit I, Services Hospital, Lahore from February 2021 to February 2022. After informed consent, patients were selected by probability sampling technique and randomized in two groups. Total 140 cases sample size is calculated with 80% power of study, 95% confidence level, 5% significance level and taking mean fasting glucose level (5.33±0.72 mmol/L) vs (5.71±0.87 mmol/L) in Detemir and NPH groups respectively. Women with age range of 18 to 40 years with Singleton pregnancy with GDM as per operational definition and those with uncontrolled blood sugar level after diet and exercise and with tablet metformin 500mg TDS were included in this study. All patients with cardiac, renal or liver diseases as per medical record and lab investigations or known diabetic patients and known allergy to insulin and its derivatives were excluded from the study. Patients willing to take part in the study presenting in OPD were asked to present next day with 08 hours fasting as per WHO guidelines. Study participants were admitted in antenatal wards for control of blood sugar level. Their sociodemographic details like name, age, gestational age, body mass index (BMI) and parity were noted on predesigned proforma. Being a tertiary care public hospital, all laboratory tests and expenses were provided free of cost and all study research personnels gave their services voluntarily. In group A, patients received insulin detemir plus Novolin R. In group B, patients received insulin NPH plus Novolin R. At baseline and after 3 weeks of treatment, fasting and post-prandial sugar levels were checked by glucometer. Both groups were compared for mean change in blood sugar level. Patients were counselled for blood sugar monitoring importance and followed till delivery. Data was analyzed using SPSS version 25 for the mean±SD for the quantitative variables like age, gestational age, BMI, pre-treatment and post-treatment blood sugar level. Both groups were compared for mean change in fasting glucose level and post prandial blood sugar level after three weeks by using independent samples t-test and Anova. Outcome of the study was assessed in terms of Mean change in Fasting blood glucose level at baseline and after 3 weeks of treatment, after 8 hours fasting, in terms of mg/dl and mean change in postprandial blood glucose level at baseline and after 3 weeks of treatment, after 1 hour of taking some meal, in terms of mg/dl.

## Results

In detemir group, the mean age of females was 29.24±7.19 years. In NPH group, the mean age of females was 29.61±6.31 years (Table-1).

**Table 1: Descriptive statistics of gestational age, age and BMI of patients.**

| *Variable* | | *Detemir (n=70)* | *NPH (n=70)* |
|---|---|---|---|
| Gestational Age (weeks) | Mean | 29.81 | 30.04 |
| | SD | 3.85 | 3.77 |
| | Min | 24 | 24 |
| | Max | 36 | 36 |
| Age (years) | Mean | 29.24 | 29.61 |
| | SD | 7.19 | 6.31 |
| | Min | 18 | 19 |
| | Max | 40 | 40 |
| BMI (kg/m$^2$) | Mean | 31.73 | 30.90 |
| | SD | 4.56 | 3.90 |
| | Min | 24.30 | 24.60 |
| | Max | 39.90 | 38.10 |

SD: Standard Deviation, Min: Minimum, Max: Maximum

In detemir group, the mean change in fasting blood sugar level of females was 57.40±20.16 g/dl. In NPH group, the mean change in fasting blood sugar level of females was 50.31±18.75 g/dl. The difference in both groups was significant ($p$ <0.05). In detemir group, the mean change in post-prandial sugar level of females was 80.44±33.44 g/dl. In NPH group, the mean change in post-prandial sugar level of females was 62.93±36.96 g/dl the difference in both groups was significant ($p$ <0.05) (Table-2).

There were 36 (25.7%) females who were primigravida, 17 (12.1%) females had parity 1, 40 (28.6%) had parity 2, 36 (25.7%) had parity 3 and 11 (7.9%) had parity 4 (Figure).

The data was stratified for, age, gestational age and BMI of females. The difference was

**Table 2: Comparison of fasting and post-prandial blood sugar at presentation, after 3 weeks and change in fasting blood sugar after treatment.**

| Blood Sugar Category | | Group Detemir (n=70) | | | Group NPH (n=70) | | | p-value |
|---|---|---|---|---|---|---|---|---|
| | | Baseline | After 3 weeks | Change | Baseline | After 3 weeks | Change | |
| Fasting | Mean | 156.74 | 99.34 | 57.40 | 155.01 | 104.70 | 50.31 | 0.033 |
| | Std. Dev. | 16.80 | 16.82 | 20.16 | 18.81 | 18.97 | 18.75 | |
| Post- prandial | Mean | 222.44 | 142.00 | 80.44 | 210.90 | 147.97 | 62.93 | 0.004 |
| | Std. Dev. | 37.88 | 15.74 | 33.44 | 38.39 | 17.05 | 36.96 | |

**Table 3: Comparison of change in fasting & post-prandial blood sugar after treatment in age and BMI strata.**

| Variable | | Fasting Sugar Level | | p-value | Post-prandial Sugar Level | | p-value |
|---|---|---|---|---|---|---|---|
| | | Detemir n (Mean±SD) | NPH group n (Mean±SD) | | Detemir n (Mean±SD) | NPH n (Mean±SD) | |
| Age Group (years) | 18-29 | 34 (53.53±18.42) | 37 (48.68±17.68) | 0.261 | 34 (79.88±31.25) | 37 (63.03±34.34) | 0.035 |
| | 30-40 | 33 (61.06±21.29) | 36 (52.15±20.01) | 0.079 | 33 (80.97±35.20) | 36 (62.82±40.23) | 0.052 |
| Gestational age (Weeks) | 24-28 | 28 (58.32±22.08) | 23 (49.74±20.18) | 0.158 | 28 (84.11±35.95) | 23 (72.04±40.73) | 0.267 |
| | 29-32 | 21 (55.19±20.61) | 24 (50.50±18.24) | 0.447 | 21 (85.24±33.16) | 24 (58.8±37.54) | 0.017 |
| | 33-36 | 21 (58.38±17.68) | 23 (50.43±18.63) | 0.155 | 21 (70.76±29.54) | 23 (58.04±31.84) | 0.178 |
| BMI | Normal | 6 (53.50±18.53) | 2 (41.00±33.94) | 0.510 | 6 (78.00±44.93) | 2 (60.00±42.43) | 0.638 |
| | Over-Weight | 24 (54.71±17.02) | 26 (46.69±19.33) | 0.128 | 24 (76.75±34.29) | 26 (57.67±41.05) | 0.082 |
| | Obese | 40 (59.60±22.19) | 42 (53.00±17.77) | 0.140 | 40 (83.03±31.78) | 42 (66.31±34.62) | 0.026 |

significant in this stratum (age group 18-29 years) ($p$ <0.05). However, in other age strata the difference was insignificant in this stratum ($p$ >0.05). In females with normal BMI, the mean change in post-prandial sugar level was 78.00±44.93 mg/dl with detemir while 60.00±42.43 mg/dl with NPH. Table-3 shows that difference is not significant ($p$ =0.638). In overweight females, the mean change in post-prandial sugar level was 76.75±34.29 mg/dl with detemir while 57.67±41.05 mg/dl with NPH. The difference was insignificant in this stratum ($p$ >0.05). In obese females, the mean change in post-prandial sugar level was 83.03±31.78 mg/dl with detemir while 66.31±34.62 mg/dl with NPH. The difference was significant in this stratum ($p$ <0.05) (Table-3).

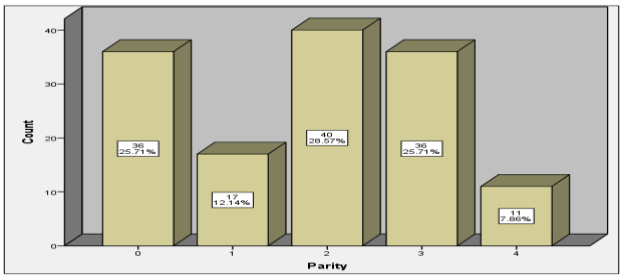


**Figure: Distribution of parity. (n=140)**

## Discussion

Participants in both treatment arms demonstrated significant improvements in glycemic parameters. In the Detemir group, the mean reduction in fasting blood glucose was 57.40 ± 20.16 mg/dL**,** whereas in the NPH group it was 50.31±18.75 mg/dL, with the between-group difference reaching statistical significance. Similarly, the mean decrease in post-prandial glucose in the Detemir group was 80.44±33.44 mg/dL, compared to 62.93±36.96 mg/dL in the NPH group, and this difference was also statistically significant. These findings suggest a greater magnitude of glycemic improvement in female patients treated with Detemir relative to NPH insulin.

The use of insulin is a well-established standard in pharmacotherapy. Both NPH and soluble human insulin have a long history of proven effectiveness, while recent experiences with novel insulins have shown promising results.[8] This type of insulin is considered intermediate-acting and can be administered twice a day. Due to its significant peak effect and variable absorption, there is a notable risk of hypoglycemia.[9] However, the safety profiles of recent insulin analogues have enabled their use during pregnancy with minimal risk of hypoglycemia, ensuring good glycemic control. Insulin detemir, a long-acting insulin approved by the US Food and Drug Administration in 2012, has demonstrated excellent efficacy in pregnancy for maintaining glycemic control and reducing hypoglycemic episodes.[10]

In China, both obstetricians and patients have expressed concerns regarding the safety of insulin use during pregnancy. To address this, data on the treatment of diabetes with Insulin detemir are being provided.[11]

In our trial, we observed that with detemir, the mean change in fasting blood sugar level was 57.40±20.16 mg/dl, while with NPH, the mean

change in fasting blood sugar level was 50.31±18.75 mg/dl with significant ($p$ <0.05) difference. It was also observed that with detemir, the mean post-prandial sugar level was reduced from 222.44±37.88 g/dl to 142.00±15.74 mg/dl, while with NPH, the mean post-prandial sugar level was reduced from 210.90±38.39 g/dl to 147.97±7.05 mg/dl. The difference in both groups was significant ($p$ <0.05).

As compared to NPH, insulin detemir shows good efficacy. A study in China showed that after one week of treatment with insulin detemir versus NPH (both with combination of Novolin R) for GDM showed that insulin detemir proved more effective in reducing hyperglycemia i.e. change in fasting glucose level (mmol/L) was 1.51±1.41 versus 1.15±0.83 for detemir and NPH groups respectively, $p$ value <0.001.[5]

Ji et al., also found after one week of therapy, the detemir group's fasting glucose level was significantly lower than the NPH group, and the duration to attain the target glycemic level ($p$-value < 0.001). The mean fasting glucose level was 5.33±0.72 mmol/L with detemir while 5.71±0.87 mmol/l with NPH ($p$ <0.01) and mean decrease in fasting glucose level was reported as 1.51±1.41 vs. 1.15±0.83, respectively, which was statistically significant ($p$ =0.018). Similarly, post-prandial sugar was 6.73±0.79 mmol/l vs. 7.38±0.80 mmol//, and mean change was observed as 2.66±1.65 mmol/l vs. 2.17±1.59 mom/l/l, respectively ($p$ =0.022). Researchers concluded that Detemir, compared to NPH, was able to manage blood glucose and attain objectives faster and more efficiently, resulting in fewer injections and lower risk of post-injection hypoglycemia in pregnancy without causing unfavorable delivery outcomes. As a result, detemir might be the ideal basal insulin for GDM who need insulin, and it would be worthy of promotion in healthcare situations.[11,12]

Khalid et al. reported that efficacy (HbA1c <6.0% till 36$^{th}$ week of pregnancy) was achieved in 49.3% cases with determine vs. 27.5% cases with NPH, p-value=0.001).[13] Detemir is significantly more effective than NPH for management of pregnant females presenting with GDM. In another comparative effectiveness trial, use of detemir leads to less chances of adverse feto-maternal outcomes than NPH.[13,14] Considerable controversy exists between various studies regarding this subject. Some studies showed that insulin detemir and NPH did not differ in terms of glycemic control and risks of hypoglycemia.[14] Mathiesen et al., reported in a randomized trial conducted in 2012 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).[15,16] Despite significant disparities in the two groups' blood glucose levels, Amini et al. determined that there were no meaningful differences between them. Detemir outperformed NPH in terms of patient's gestational age and BMI. as well as length of hospitalisation.[16]

In clinics, NPH is the most often utilized intermediate-acting insulins. Long-acting insulin analogues, like insulin glargine and detemir, are being introduced into clinical practice, and their safety and effectiveness must be shown quickly. There is, however, a scarcity of compelling evidence in this regard.[17,18]

According to a cohort study of 91 pregnant females with GDM, detemir was reported to have superior outcomes than glyburide. Detemir's efficacy and safety were recently studied in a randomized experiment that included both GDM and type 2 diabetes. The results revealed that detemir's glycemic control efficacy was comparable to that of NPH, and that hypoglycemia episodes were dramatically reduced when the short-acting insulin as part was supplemented.[18]

Whereas the total dosage of detemir was larger than NPH, this was due to detemir's lower affinity for the insulin receptor than NPH.[19] This could be because of detemir's unusual hexametric structure and it's reversible interaction with serum albumin that greatly increased the action phase.[19] When administered a hypoglycemic medication with detemir, these improvements combined made females feel more content and cooperative. In meta-analysis by Athanasiadou et al showed that insulin detemir was associated with less maternal hypoglycemic events and decreased risk for prematurity compared with NPH insulin.[20] The limitations of study were methodological variations, confounding factors, and logistical issues. Further studies, including longer and more comprehensive scales should be carried out to better understand the associations found in the present study

## Conclusion

Detemir was found to be more effective in controlling blood sugar level than NPH in pregnancy. Now in future, we will recommend to prescribe detemir instead of NPH to control glycemic level in pregnancy and prevent obstetrics complications related to high glycemic index.

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**Availability of Data:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Ethical Approval:** The Institutional Review Board of Services Institute of Medical Sciences, Lahore approved the study via letter no. IRB/2021/1384/SIMS.

**Conflict of Interest:** None declared.

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