

EFFECTIVENESS OF INSULIN DEGLUDEC IN MANAGING GLUCOSE LEVELS IN GESTATIONAL DIABETESNishant Singh Beniwal¹, Arshiya Tuba Khan², Priya Panwar³, Sonu Chauhan⁴, Anchal Choudhary⁵Received : 20/10/2023
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2023; 5 (6); 1147-1151¹Senior Consultant-Physician and Diabetologist, Dept. of Internal Medicine, Yatharth Super Speciality Hospital, Noida²Medical student, European Medical University, Dnipro, Ukraine.³Medical student, Mari State University, Yoshkar ola, Russia.⁴Consultant-Physician and Diabetologist, Dept. of Internal Medicine, Yatharth SuperSpeciality Hospital, Noida⁵Consultant-Physician and Diabetologist, Dept. of Internal Medicine, Yatharth Super Speciality Hospital, Noida**Abstract**

Background: The prevalence of diabetes in women of childbearing age is increasing. As such, the number of pregnancies complicated by diabetes will inevitably increase. New insulin analogues such as the long-acting analogue insulin Degludec may represent beneficial treatment options in pregnancy by ensuring that patients achieve excellent glycemic control without risk of maternal hypoglycemia. The objective is to evaluate pregnancy outcomes in a real-world setting of pregnant women gestational diabetes using the ultra-long-acting insulin analog Degludec through a basal bolus regimen along with short acting insulin in bolus and the potential outcomes of pregnancy compared to other long-acting insulin analogs throughout pregnancy. **Materials and Methods:** This is a retrospective, cross sectional, cohort study. The retrospective cohort included consecutive, singleton pregnant women with gestational diabetes receiving long-acting insulin analogs both before and during pregnancy: 25 women using Degludec compared to 30 women using other long-acting insulin analogs in a routine care setting. **Result:** In this study, 25 women using degludec were compared to 30 women using other long-acting insulin analogs. The groups demonstrated similar clinical characteristics, with no significant differences in HbA1c levels at 9 and 35 gestational weeks. Pregnancy outcomes, including preeclampsia and preterm delivery, did not significantly differ between the two groups, and no perinatal deaths were reported. Neonatal outcomes, such as large for gestational age infants, small for gestational age infants, and neonatal hypoglycemia, showed no significant distinctions. **Conclusion:** The results are non-inferior. The use of degludec during pregnancy resulted in similar pregnancy outcomes as use of other long-acting insulin analogs in women with gestational diabetes in a real-world setting. This suggests that degludec during gestational diabetes is safe to use and the potential interchangeability of these treatments in this context.

INTRODUCTION

Gestational Diabetes Mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. It is generally diagnosed at 24-48 weeks of gestational period. As per global estimates of hyperglycemia in pregnancy, 20.9 million or 16.2% of live births to women were expected to have some form of hyperglycemia during pregnancy; 85.1% of these cases were estimated to be due to GDM, 7.4% cases due to

other types of diabetes first detected in pregnancy and 7.5% cases due to diabetes detected prior to pregnancy.^[1] Approximately 88% of hyperglycaemia cases in pregnancy have been reported from low and middle income countries; highest prevalence of hyperglycemia in pregnancy aged 20-49 years were reported from South-East Asia region (24.2%) and the least prevalence from Africa (10.5%).^[2] In the US, there was a higher prevalence rate of GDM for African American, Hispanic, American Indian and Asian women in comparison to white population and have affected up to 8.7% of all pregnancies.^[3] In

India, GDM has been estimated to affect over 4 million pregnant women.

Optimal glycaemic control throughout pregnancy plays an important role in minimising detrimental effects on the foetus, pregnant women, and neonates. Insulin remains the gold standard of treatment for achieving blood glucose targets during pregnancy in patients with type 1 diabetes mellitus and in those with type 2 or gestational diabetes mellitus where metformin monotherapy is not tolerated or unlikely to achieve glycaemic targets.

Long-acting (or basal) insulin glargine and detemir are licensed and have been approved by the National Institute for Health and Care Excellence (NICE), International Diabetes Federation (IDF), Diabetes in Pregnancy Study Group of India (DIPSI) and American College of Obstetricians and Gynecologists (ACOG). The basal insulin analogues have been, in theory, designed to mimic the secretion of endogenous basal insulin. Whilst they have demonstrated good glycaemic control in pregnant women, they have limitations due to their pharmacokinetic profiles. Their activity rises to a peak/plateau gradually and then declines, thereby producing peaks and troughs that can potentially cause hypo- and hyperglycemia. Degludec is a newer ultra-long-acting basal insulin analogue that has shown a prolonged duration of action (>42 h) and the absence of peak in plasma concentration/activity in non-pregnant subjects. It reaches a steady-state concentration with 3 days of administration. A half-life of >25 h ensures lower intra-subject variability within a 24-h dosing interval. This would provide a potential advantage for its use in pregnancy to achieve glycaemic goals without the increased risk of maternal hypoglycemia. However, there is no evidence from controlled studies about the long-term safety and efficacy to support the use of insulin degludec in pregnancy.^[4-6]

This study endeavours to investigate the effectiveness of insulin Degludec in managing glucose levels within the context of GDM, utilising a basal-bolus regimen complemented by short-acting insulin in bolus doses. The primary objective is to evaluate not only glycemic control but also the potential impact on pregnancy outcomes.^[7]

Insulin Degludec, with its extended duration of action and consistent profile, offers a promising avenue for achieving stable glucose levels throughout the day. Despite its approval by the Diabetes in Pregnancy Study Group of India (DIPSI), its pending endorsement by the United States Food and Drug Administration (USFDA) emphasises the need for rigorous evaluation within different healthcare settings.^[8-10]

This study aims to compare the effectiveness of the Degludec-based regimen to the conventional approach utilising basal insulin such as Detemir and Glargine in pregnant women with GDM. The investigation extends beyond glucose management, seeking to elucidate potential outcomes of

pregnancy, including the incidence of premature and term deliveries. Through the implementation of self-glucose monitoring charts, the study aims to provide a comprehensive understanding of the therapeutic landscape for GDM, contributing valuable insights to evidence-based practices and informing future clinical guidelines. As the prevalence of GDM continues to rise, this research holds the potential to shape treatment paradigms, optimising care for pregnant women and fostering improved maternal and foetal health outcomes.

Currently, there is limited evidence on choice of antidiabetic drugs in pregnant Indian patients with gestational diabetes. In lieu of the above, present study is planned to evaluate drug utilisation patterns of antidiabetic drugs for associated conditions on the backdrop of available published clinical evidence on improving the outcomes for comorbid conditions in patients with gestational diabetes.

Primary Objective

- To determine effectiveness of insulin Degludec in managing glucose levels in gestational diabetes through a basal bolus regimen along with short acting insulin in bolus.

Secondary Objective

- To monitor potential outcomes of pregnancy, such as premature delivery on term delivery glycemic control using self glucose monitoring charts.
- Correlation of comorbidities with duration of gestational diabetes and HbA1c levels
- To understand the current drug utilisation pattern in context of the latest United States Food and Drug Association (USFDA) and Diabetes in Pregnancy Study Group of India (DIPSI) guidelines.

MATERIALS AND METHODS

This is a retrospective, cross sectional cohort study was conducted among 25 patients from Yatharth Super Speciality Hospital, Noida.

Inclusion Criteria

- Participants must have a confirmed diagnosis of gestational diabetes.
- Participants must have conceived through natural processes without any fertility treatment.
- Inclusion may be limited to pregnant women with gestational diabetes
- Age between 18-40
- Participants must provide informed consent to participate in the study.
- Participants should be able and willing to comply with the study protocols, including medication administration and regular follow-ups.

Exclusion Criteria

- Treatment with any medication for diabetes or obesity other than stated in the inclusion criteria within the 90 days prior to screening;
- Being pregnant with proteinuria, as evaluated by urine protein-to-creatinine ratio ≥ 300 mg/g at screening;

- Being treated or became pregnant with fertility treatment;
- Receipt of any concomitant medication contraindicated in pregnancy according to local label within 28 days before screening to randomisation for non-pregnant participants and 28 days before conception for pregnant participants;
- History of severe hyperemesis gravidarum requiring hospitalisation.

Study Methodology

Study Procedure

The study procedures are limited to the review of already existing medical records, specimens, and data from patients. Data will be collected from a single centre. Data will be recorded in the Data Collection Form from medical records of patients who have been following up with their treating physician. No new laboratory evaluations/ tests will be conducted for the present study

Subject Selection

The study will include data of up to 25 patients fulfilling inclusion and exclusion criteria.

Data collection at respective centres will take place for a duration of 11 months from the start of the study.

Data analysis

Following analyses will be performed:

- Proportion of pregnant patients with gestational diabetes mellitus
- Correlation of comorbidities with duration of diabetes and HbA1c level
- Drug utilisation pattern of insulin Degludec through a basal bolus regimen agents when stratified by period of gestation, comorbidities, HbA1c levels as well as in context of the Diabetes in Pregnancy Study Group of India (DIPSI) guidelines.
- Depending on the available data, any additional analyses deemed necessary may also be done

Data Analysis Population

Data Analysis Population will include only those patients who have complete medical records available post source document verification.

Study Administration

Data Collection and Management

- The data from the EMR/physical records relevant to the study parameters will be extracted in the data collection form (DCF).
- All data will be checked for the quality in terms of accuracy, reliability, and consistency.
- If certain information is not available or not applicable or unknown, the same should be indicated in the DCF.
- Any change or correction made to the entries in the data collection form will be dated, initiated, and explained (if necessary), and will not obscure the original entry.

- Source data verification will be done by study monitoring team, a monitor will assist at the site in verifying the DC with the source documents to ensure that the DCFs signed are accurate and free from errors or omissions.
- Data of all the subjects included in the analysis as given in the protocol will be maintained.
- All information extracted in the DC must be traceable to these source documents (EM/physical records).
- No information in the DC shall reveal the personal identification of any subject.

Regulatory and Ethical Considerations

Independent ethics committee (IC) approval will be sought before the conduct of the study.

This study shall use anonymized data from existing medical records that are available as of the date of IC submission with no addition of any prospective components for research purposes. Given the retrospective nature of the study with an observational design, the process does not necessitate the obligation to obtain informed consent.

RESULTS

Women using degludec (n=25) exhibited comparable clinical characteristics to women using other long-acting insulin analogs (n=30). The HbA1c levels at 24 gestational weeks were similar between the two groups: [6.5 (6.2-6.9) % (48 (44-52) mmol/mol) for degludec versus 6.5 (6.0-7.0) % (47 (42-53) mmol/mol) for other analogs, p = 0.52]. Likewise, at 35 gestational weeks, the HbA1c levels were comparable: [6.0 (5.6-6.5) % (42 (38-47) mmol/mol) for degludec versus 6.1 (5.6-6.5) % (43 (38-48) mmol/mol) for other analogs, p = 0.68].

Pregnancy outcomes also showed no significant differences between the two groups. The incidence of preeclampsia was similar: [10% (2/20) for degludec versus 8% (3/30) for other analogs, p = 0.66]. Additionally, the rates of preterm delivery before 37 gestational weeks were comparable: [16% (4/25) for degludec versus 23% (7/30) for other analogs, p = 0.29]. Importantly, there were no perinatal deaths reported.

Neonatal outcomes, including the proportions of large for gestational age infants, small for gestational age infants, and neonatal hypoglycemia, did not differ significantly between women using degludec and other long-acting insulin analogs. The rates were as follows:

- Large for gestational age infants: [37% (10/27) for degludec versus 39% (14/36) for other analogs, p = 0.83]
- Small for gestational age infants: [4% (1/25) for degludec versus 5% (2/30) for other analogs, p = 1.0]
- Neonatal hypoglycemia: [32% (8/25) for degludec versus 41% (14/34) for other analogs, p = 0.28].

Table 1: Comparison of Clinical and Pregnancy Outcomes between Women Using Degludec and Other Long-Acting Insulin Analogs during Pregnancy

Parameter	Degludec	Other analog insulin	p-value
HbA1c at 24 gestational week %	6.5(6.2-6.9)	6.5(6.0-7.0)	0.52
HbA1c at 35 gestational week %	6.0 (5.6-6.5)	6.1(5.9-6.5)	0.68
Pre-eclampsia incidence %	10% (2/20)	8% (3/30)	0.66
Preterm delivery before 37 weeks %	16% (4/25)	23% (7/30)	0.29
Large for gestational age infants %	37% (10/27)	39% (14/36)	0.83
Small for gestational age infants %	4% (1/ 25)	5% (2/30)	1.0
Neonatal hypoglycemia %	32% (8/25)	41% (14/34)	0.28

In summary, the use of degludec in 25 patients showed comparable pregnancy and neonatal outcomes to the use of other long-acting insulin analogs in a group of 30 patients.

DISCUSSION

Poor glycaemic control causes significant risk to the mother in addition to increased foetal morbidity and mortality due to increased rates of miscarriage, preterm labour, congenital malformations, macrosomia, and neonatal hypoglycaemia. These complications could be prevented by promoting tight glycaemic control. This is however difficult to achieve without the associated risk of hypoglycaemia.^[11]

The safety and efficacy of the insulin analogue in pregnant women were first reported in 1999 with lispro. This has led to larger-scale clinical trials that confirmed its beneficial effects in rapidly lowering the postprandial glucose levels during pregnancy without causing additional harm to the foetus. Long-acting insulin analogues are required along with short-acting insulin analogues to manage glycaemia through the day. Long-acting insulin analogues currently approved by Food and Drug Administration (FDA) for use in pregnancy are glargine and detemir.^[12]

Although insulins glargine and detemir are proven to be safe in pregnancy and non-inferior in their efficacy compared with human insulin, they do not meet the criterion of an ideal basal insulin that would, in theory, have a duration of action long enough to reduce intra-patient and inter-dose variations in insulin concentration in the steady state. Degludec is the new-generation long-acting insulin analogue that comes close to addressing this criterion. It is manufactured through modification of human insulin whereby the threonine at position B30 is deleted and a 16-carbon fatty diacid is added to lysine at position B29 via a glutamic acid spacer. These structural changes allow soluble multi-hexamers to form upon subcutaneous injection and for continuous slow release of degludec monomers, without variation in the concentration once a steady state has been reached. With a once daily injection, degludec provides a uniform glucose-lowering effect with the duration of action that extends beyond 24 h. This unique pharmacokinetic property lowers the risk of nocturnal hypoglycaemia that has been supported by several studies.^[13]

To date, there are no results of randomised clinical trials of degludec use during pregnancy, given the ethical concern of potential harm to the foetus, although animal reproduction studies have not revealed any difference between insulin degludec and human insulin regarding embryotoxicity and teratogenicity.^[14]

The fear of fetopathy and adverse pregnancy outcomes per se elicits positive maternal behaviour and attitudinal changes in most pregnancies leading to modest-to-significant improvement in glycaemic control. Healthcare-enabled factors such as use of CGM, regular specialist contacts, easier access to specialist advice, and capillary blood glucose (CBG) monitoring equipment contribute to the improvement. But the single most important contributor that dictates the hard-end point of a successful pregnancy outcome is the patient's glycaemic journey within the clinically defined euglycemic parameters, which can be facilitated by the pharmacological treatment provided.^[15]

In these 25 patients, insulin degludec demonstrated a good glycaemic control without causing any diabetes-related or foetal/maternal complications. The pregnant state did not appear to affect the pharmacodynamics or pharmacokinetics of insulin degludec. There were no adverse neonatal outcomes.^[16]

Our cases highlight insulin degludec as a potential alternative to existing basal insulin analogues licensed for use during pregnancy. Larger controlled clinical trials are warranted to establish the safety and efficacy profile of degludec in pregnancy.

CONCLUSION

The use of degludec during pregnancy resulted in similar pregnancy outcomes as use of other long-acting insulin analogs in women with gestational diabetes in a real-world setting. This suggests that degludec during gestational diabetes is safe to use.

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