Case Report

Insulin desensitization in a patient with gestational diabetes mellitus and the role of continuous positive airway pressure (CPAP) in the management of elevated morning blood glucose

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Abstract

A 31-year-old lady with gestational diabetes started to develop an allergic reaction to all types of insulin injections. It seems that the allergy was related to one of the preservatives in the injections. Different approaches were attempted without significant improvement. She was then admitted for 12 hours for insulin desensitization. Desensitization protocol was administered under strict supervision. There were no significant complications. Patient symptoms improved significantly afterwards. Also, the persistent elevation of the morning blood glucose triggered investigations for obstructive sleep apnea. Continuous Positive Airway Pressure (CPAP) therapy was helpful to reduce the morning blood glucose to the target range.

Case

This 31-year-old lady, Gravida 2 Para 1, had a history of gestational diabetes. During her last pregnancy, Gestational diabetes was managed with diet and exercise, and the patient did reasonably well with no fetal related or maternal complications. After her first delivery and the postpartum period, her blood glucose levels and hemoglobin A1c both within normal ranges. The patient became pregnant again, and screening for gestation diabetes was done around the ninth week of pregnancy, which was positive for gestational diabetes. During her first visit to the gestational diabetes clinic, her vitals were normal, and her physical examination was unremarkable except for being obese with a Body Mass Index (BMI) of 33.

Initially, the patient was managed with a diet, including caloric restriction and exercise, from gestational week nine to eleven. Her morning blood sugars were elevated above the target range. Postprandial readings were mildly elevated most of the time too. There was no evidence of increased ketones. Gestational week eleven, Insulin NPH (Isophane Insulin, Novolin NPH) was started at a low dose. The postprandial blood glucose measurements began to fall within range but not the morning readings. Insulin NPH (Isophane Insulin, Novolin NPH) dosing was increased by the diabetes education center for three consecutive visits without significantly improving morning blood glucose readings. Gestational week seventeen, Metformin (Glucophage) 250 mg orally twice daily was added and increased later to 500 mg orally twice daily. Increasing the dose of Insulin NPH (Isophane Insulin, Novolin NPH) and adding Metformin (Glucophage) did not help with elevated blood glucose readings. The patient was adherent to the diet and exercise recommendations.

As the patient's Body Mass Index (BMI) was high and she also described snoring during sleep, she was tested for obstructive sleep apnea with a level III sleep study. The study revealed evidence of increased upper airway resistance and at least mild obstructive sleep apnea as multiple diminutions of flow were not scored as events due to lack of desaturations. It was determined that if a level I polysomnogram would have been done, it would probably show some arousals matching the periods of the flow diminutions, giving a higher index into the moderate severity range. Around the twentieth week of gestation, the patient was started on Continuous Positive Airway Pressure (CPAP) therapy, automatic setting 4 to 20, and then optimizing treatment accordingly. Soon after the patient began Continuous Positive Airway Pressure (CPAP) therapy, morning blood glucose improved to fall back within the target range.

While escalating the dose of Insulin NPH (Isophane Insulin, Novolin NPH), the patient started developing a delayed reaction at the injection site. She developed a small, around 1 centimetre in diameter, erythematous papule at the site of Insulin NPH (Isophane Insulin, Novolin NPH) injection. A process of elimination was

used to identify the cause, and the patient was started on loratadine empirically. Avoiding alcohol swabs did not make any difference. Dry injection (i.e., inserting the needle without injecting any medications) did not produce any a reaction. Injecting normal saline solution did not create a reaction either. It was suspected that the patient reacted to the insulin component or the preservative used. The type of insulin was changed, and the following types were used:

- Humulin N (Insulin NPH, Isophane Insulin, Novolin NPH)
- Humulin R (Insulin Regular, Novolin Toronto)
- Lantus (Insulin Glargine)
- NovoRapid (Insulin Aspart)
- Levemir (Insulin Detemir)
- Humalog (Insulin Lispro)

The lowest reaction was with Insulin NPH (Isophane Insulin, Novolin NPH),the first type of insulin used, which still caused the patient a great deal of discomfort. The patient reported that the reaction was worse with higher doses of insulin.

Insulin desensitization was offered to the patient around gestation week twenty-four, and she was interested. After discussing the potential benefit and potential complication with the patient, she provided verbal and written consent and subsequently, arrangements for admission to the hospital were made. A protocol was created for the desensitization procedure, which was implemented in the medical inpatient unit. Please see Appendix A for details. Since the patient reported a delayed reaction, up to 3 hours after injection, the patient was monitored for 4 hours after completing all the protocol steps and then discharged home. This is to ensure she did not develop any reactions after the desensitization procedure. This is important to determine the dose that produced a reaction and resume desensitization at the lowest dose that did not produce a reaction. There were not any significant complications.

The patient reported significant improvement in her symptoms. The appearance of any reaction after Insulin NPH (Isophane Insulin, Novolin NPH) injections was rare, and when it occurred, it was delayed by more than 6 hours. When there was a reaction, it was mild and only lasted for a few hours and disappeared spontaneously without any management. The patient was happy with the results. The desensitization made it possible to increase the insulin doses without significant reactions. This was helpful in the third trimester, mainly when the patient needed more calories and higher insulin doses. There were no further complications during the pregnancy, and the patient's blood glucose was well controlled. She had an uneventful delivery of a healthy 8.5 pounds baby boy.

Discussion

Treatment of obstructive sleep apnea in patients with diabetes:

Obstructive sleep apnea can be a factor for uncontrolled Diabetes. Unfortunately, it is usually missed as a cause of difficulty in controlling blood glucose. Other factors make it challenging to investigate the disorder and treat it, as the availability of sleep labs and the cost of purchasing a positive pressure ventilation device. The hormonal disturbance caused by obstructive sleep apnea and interrupted sleep leads to increased insulin resistance. This has been demonstrated in multiple cross-sectional studies[1-5].The association between obstructive sleep apnea and Type II Diabetes has also been demonstrated in multiple studies, especially when the obstructive sleep apnea is moderate or severe[6-10]. The severity of obstructive sleep apnea has also been linked to higher hemoglobin A1c[11-13].

The mechanism of glucose metabolism dysregulation caused by sleep disordered breathing is not fully understood. It is suspected that increased sympathetic activity in patients with sleep disordered breathing plays a role in glucose dysregulation. Sympathetic nerve activity was monitored, and it was noted to be elevated compared to normal subjects[14-15]. The increased sympathetic activity has a direct effect on insulin secretions, glucose synthesis and incretins secretions. Other suggested mechanisms include systemic inflammation and activation of the hypothalamic-pituitary-adrenal axis.

Sleep-disordered breathing has been linked to Gestational Diabetes too. Pregnant women with obstructive sleep apnea have a 50% increased risk of developing Gestational Diabetes than pregnant women without obstructive sleep apnea. The risk of other disorders like preeclampsia and eclampsia is also higher in pregnant women with obstructive sleep apnea[16]. A higher micro-arousal index and higher desaturation index were associated with more elevated fasting blood glucose in pregnant women[17].

Some studies demonstrated a favourable impact of Continuous Positive Airway Pressure (CPAP) therapy on obstructive sleep apnea and gestational Diabetes[18-19]. Other studies did not reveal any difference in fasting blood glucose values or hemoglobin A1c values, mainly in patients with type II diabetes[21-23].

The common problem with all these studies is that they are not appropriately powered to demonstrate a reliable outcome. Several variables affect the results of studies investigating the effect of positive airway pressure on glycemic control. The method used in diagno-

sis, the severity of the sleep disorder, concomitant existence of other sleep disorders, adherence to positive airway pressure therapy, and positive airway pressure effectiveness in treating obstructive sleep apnea are all factors that can impact the results of such studies. Other variables include the length of the treatment period and how the effect on glucose metabolism was measured.

Generally, it does not seem that there is strong evidence of better glycemic control with Continuous Positive Airway Pressure (CPAP) therapy in patients with obstructive sleep apnea and gestational diabetes[21]. The effect of CPAP on glycemic control in gestation diabetes is still under investigation[20].

Treatment of obstructive sleep apnea during pregnancy:

According to multiple prospective cohort studies, the prevalence of obstructive sleep apnea in pregnancy is estimated to be between 3.6 and 26.7%24-25.The safety of positive pressure ventilation during pregnancy has been established in various studies, too 26-27. Untreated obstructive sleep apnea has been associated with multiple maternal morbidities, including eclampsia, cardiomyopathy, and pulmonary embolism 28-29. It does not seem that there is any measurable effect of obstructive sleep apnea on the fetus. However, some cohorts show a signal toward retarded fetal growth and maybe intrauterine fetal death. Hence, the general recommendation is to treat obstructive sleep apnea with positive pressure therapy during pregnancy 30-31. In the case describes-above, the patient did not have any significant symptoms other than the elevated blood glucose, which, in my opinion, was an indication to start treatment.

Insulin desensitization:

The desensitization procedure is very well established for multiple medications. For example, the Acetyl Salicylates desensitization protocol is well established across all hospitals in Nova Scotia, as it is frequently used for patients who will require treatment of cardiovascular events[32]. Also, a similar protocol has been established for different antibiotics. There is a published insulin desensitization protocol in previous case studies[33-34]. There is also a case report of insulin desensitization in a pregnant lady[35]. In this case, the protocol is very similar except for monitoring and intravenous administration of Dextrose 5% in water during the procedure to prevent any significant hypoglycemia.

Before attempting desensitization, it is essential to rule out other causes and establish a cause-effect relationship between insulin and the allergic reaction.

Hypersensitivity to preservatives, especially protamine, seems to be more common than hypersensitivity to injectable insulin. Due to the unavailability of injectable insulin without preservatives, we could not determine if the allergic reaction is due to the insulin or the preservatives.

By attempting different insulin formulations, some of the potential allergens were excluded. For example, the patient developed a reaction to Lantus (Insulin Glargine). Lantus (Insulin Glargine) does not contain protamine. It was determined then that the patient either has hypersensitivity to insulin or another preservative like Metacresol, Glycerine or Zinc. Phenol was excluded using the same process of elimination.

Monitoring was an essential part of the protocol. It focused on monitoring for allergic reactions and included hypoglycemia and frequent glucose monitoring to avoid any potential complications.

Conclusion

Gestational Diabetes is considered one of the high-risk conditions due to its multiple effects on the mother and the fetus. Adapting different treatment modalities like Continuous Positive Airway Pressure (CPAP), when appropriate, might mitigate using high doses of insulin and other hypoglycemic agents, which might have their side effects. CPAP therapy is considered safe during pregnancy.

Insulin desensitization is useful in the treatment of insulin hypersensitivity in gestational Diabetes. Precautions to avoid severe hypersensitivity reactions, hypoglycemia, and hyperglycemia are necessary. Close monitoring is critical to ensure the safety of the procedure.

Patient Consent

The case report was discussed with the patient. The patient had the opportunity to read the content of the case report. The patient provided verbal and written consent to publish the case in any medical journal without any preservations. The patient consented to publish any related data, images, photos, records, or any other materials when applicable. The patient understands that the Material will be published without the patient's name attached; however, complete anonymity cannot be guaranteed. Somebody somewhere may recognize the patient. The Material may show or include details of the patient's medical condition or injury, and any prognosis, treatment, or surgery that the patient has, had, or may have in the future. The article may be published in a journal that is distributed worldwide. The article, including the Material, may be the subject of a press release and may be linked to social media and/or

used in other promotional activities. Once published, the article may also be available on other websites. The text of the article will be edited for style, grammar, and consistency before publication. The patient will not receive any financial benefit from the publication of the article. This includes publication in English and translation, in print, in digital formats, and in any other formats that may be used. The article may appear in local editions of journals or other publications. The patient can revoke the consent at any time before publication, but once the article has been committed to publication, it will not be possible to revoke the consent. The patient has had the opportunity to comment on the article, and I am satisfied that the comments, if any, have been reflected in the article.

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Appendix A

Insulin Desensitization Protocol in Gestational Diabetes:

Insulin preparation:

Insulin NPH (Isophane Insulin, Novolin NPH) was used during the whole protocol. The hospital pharmacy prepared different concentrations. Doses less than 1 ml in volume were diluted with normal saline solution, so the end volume in 1 ml.

Patient preparation and monitoring:

The patient was advised to administer the usual night dose of Insulin NPH (Isophane Insulin, Novolin NPH) at the same time it was initially prescribed. The patient was advised not to administer any Insulin NPH (Isophane Insulin, Novolin NPH) the morning of the procedure and arrive 1 hour before the procedure's scheduled start time. Basal vital signs were measured, and baseline blood glucose measurements were obtained using both an intravenous sample and capillary sample at the same time. Dextrose 5% in water was started intravenously at 75 ml per hour and continued to be infused for one hour after the last dose of insulin was injected.

Vital signs were measured hourly. Blood glucose was measured hourly unless it was less than five or more than ten mmol/L. If the blood glucose was less than five or more than ten mmol/L, glucose was checked every 30 minutes. SPO2 was continuously monitored. Inspection of the site of injections was done hourly. If the blood glucose is lower than 4, 10 ml of Dextrose 25% in water should be injected. If the blood glucose value is more than 12, the infusion rate should be decreased to 25 ml per hour.

Questions about the following were also asked hourly to monitor for hypoglycemia or hypersensitivity reaction:

- Sweating
- Irritability or nervousness
- Tremors
- Confusion
- Tachycardia
- Feeling hungry
- Light-headedness or blurring of vision
- Nausea
- Skin rash
- Chest tightness
- Shortness of breath
- Itching
- Wheezing
- Swelling

Insulin injection procedure:

1. Intradermal 1 ml of normal saline solution was injected as a reference. The site was marked "S" for saline.
2. Intradermal 0.001 units of Insulin NPH (Isophane Insulin, Novolin NPH) injected 1 cm away from the previous injection and marked "1".
3. The dose was multiplied by 10 for the subsequent injections until a dose of 1 unit was reached. The same procedure of spacing and marking was used. The dose of 1 unit of Insulin NPH (Isophane Insulin, Novolin NPH) was also injected intradermally.
4. Doses of more than 1 unit were injected subcutaneously.
5. Monitoring for skin reaction was done hourly before each subsequent injection. If there is a reaction, the last dose that did not produce a reaction was used. The site was marked with the same number of the dose that did not produce a reaction.
6. Once 1 unit of Insulin NPH (Isophane Insulin, Novolin NPH) was injected, each dose was double that of the previous dose. E.g., 1 unit, 2 units, 4 units, until the desired dose of Insulin NPH (Isophane Insulin, Novolin NPH) required for glycemic control is reached.
7. The patient should be monitored for 4 hours after the last injection.
8. The patient should start the initially prescribed dose of Insulin NPH (Isophane Insulin, Novolin NPH) within 12 hours after completing the desensitization protocol.