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Review Article

INSULIN TREATMENT FOR GESTATIONAL DIABETES MELLITUS

*** Anak Agung Gde Kiki Sanjaya Dharma, I Gusti Ayu Made Putri Hitasari, William Alexander Setiawan**

Obstetric and Gynecology Department, Prof. Dr. I.G.N.G. Ngoerah Hospital/Medical Faculty of Udayana University, Bali, Indonesia.

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ABSTRACT

Gestational diabetes is one of the most common pathologies in pregnancy that can potentially cause other complication, both to the mother and the fetus. This condition is considered as a global health problem with Asia having the highest prevalence. A few factors affecting this condition are maternal age and ethnicity. Several managements can be chosen but the safest treatment uses insulin. Insulin is the only therapy that do not cross the placenta and most types have no effect on pregnancy and fetal/neonates.

Keywords: Gestational diabetes, maternal dyslipidemia, Pre-eclampsia, hyperinsulinemia

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as a glucose intolerance which is first recognized in 24th week of pregnancy, excluding patients meeting type 2 diabetes mellitus' criteria, and blood glucose levels returning to normal after pregnancy.[1,2] It is a state of high blood glucose or hyperglycemia, which according to International Association of Diabetes and Pregnancy Study Groups (IADPSG) or World Health Organization (WHO)and American Diabetes Association (ADA) or American College of Obstetricians and Gynecologists (ACOG) criteria, have a fasting plasma of ≥95 mg/dL (≥5.1 mmol/L), 1-hour ≥140 mg/dL(≥10 mmol/L), 2-hour ≥120 mg/dL(8.5 mmol/L) after a 75 g oral glucose tolerance test (OGTT), and HbA1c ≥6.5%.[3,4]

The incidence and effects of GDM cause it to be global health problem, with 7% of pregnancies are diagnosed with GDM.[1] A prevalence of 14.7% worldwide, representing more than 20 million births annually.[3,5]Asians, particularly, have a high prevalence, where in Middle East is 8.8-20%, South-East Asia is 9.6-18.3%, and Western Pacific is 4.5-20.3%.[6] In Indonesia, 1.9-3.6% of pregnant women suffer from GDM.[7] During pregnancy, maternal dyslipidemia is a physiological reaction that supplies fuel and nutrition to both the placenta and the developing child. While it is typical for expectant mothers to gain body fat equal to roughly 30% of their gestational weight. The most common risk factors for GDM are obesity and overweight. Just the BMI prior to pregnancy poses a significant risk for GDM. Increased lipid synthesis in overweight and obese individuals causes lipids, primarily triglycerides, to build up in adipose tissue and other organs including the liver. Pregnancy exacerbates hepatic insulin resistance, which is elevated in obesity and raises the chance of developing GDM.[8]

Among women who are of reproductive age, GDM and PCOS are the most prevalent endocrine disorders. Chronic oligomenorrhea, hyperandrogenism, and insulin resistance are the hallmarks of polycystic ovarian syndrome (PCOS), a complex endocrine and metabolic condition. Insulin resistance and obesity are linked to PCOS, just like they are to GDM. PCOS by itself is not a risk factor for GDM, although women with PCOS who also have additional comorbidities such obesity and older mothers are more likely to develop GDM.[8,9] Pre-eclampsia is a prevalent hypertension condition that affects 2-8% of pregnancies globally. Pre-eclampsia is associated with obesity, hyperglycemia, and glucose intolerance, just like GDM [59]. Pre-eclampsia is recognized to be more likely in those with hyperglycemia. Pre-eclampsia is an independent risk factor for GDM in subsequent pregnancies.[8]

Maternal age is a common risk factor for GDM. Studies have shown that maternal age over 25-30 years old increases the risk of GDM. In a meta-analytic study examining the relationship between maternal age and risk of GDM, the authors found a linear association between risk of GDM and increasing maternal age. The study also pointed out that in the general population, Asian and European populations, the risk of GDM increased by 7.90%, 12.74% and 6.52% for each additional year after the age of 18.[9]

Several investigations have associated GDM with ethnicity. The probability of developing GDM is higher in multiple ethnic and racial groups, including Hispanic, African American, and Asian women. Women from the Korean, Chinese, and Filipino ethnic groups have a doubled probability of having GDM as compared to Caucasian or African American women. Despite the lack of understanding of the mechanisms, possible scenarios can be conceived of based on health-related predisposition, lifestyle, cultural components, and economic stressors.[8] GDM's pathogenesis is unclear, but it has been linked to hormonal abnormalities that impact insulin sensitivity and pancreatic β-cell activity. Claes Hellerström is recognized with pioneering research into pancreatic changes during pregnancy and breastfeeding in a mouse model, which began in 1963. Physiologically, insulin requirements increase during pregnancy. The increase in insulin demand is caused by increased maternal caloric intake, maternal weight gain, the presence of placental hormones such as placental growth hormone and placental lactogen, and increased prolactin and growth hormone synthesis. As pregnancy progresses, the pancreatic β-cell mass rises to meet the requirement for more insulin. GDM occurs when β-cells fail to expand and insulin production does not increase sufficiently.[10,11]

***Corresponding Author: Anak Agung Gde Kiki Sanjaya Dharma,**
Obstetric and Gynecology Department, Prof. Dr. I.G.N.G. Ngoerah Hospital/Medical Faculty of Udayana University, Bali, Indonesia.

Maternal glucose is transferred to the fetus via the placenta, and this delivery is determined by the concentration gradient between the fetus and maternal glucose levels. In the latter stages of pregnancy, the fetus diverts an increasing amount of maternal glucose to itself, resulting in a fall in maternal glucose levels. To maintain the glucose concentration gradient across the placenta between the mother and the fetus, maternal insulin resistance rises, as does hepatic glucose synthesis. To prevent the fetus from receiving too much glucose, β-cells secrete more insulin.[11,12]

Every expectant woman should get tested during the mid-trimester, which is between 24 and 28 weeks of gestation, according to the American College of Obstetricians and Gynecologists (ACOG). In certain nations, an obstetrician-gynecologists risk assessment informs the testing process. Physicians categorize risk as very high, moderate, or low. Individuals who are under 25 years old, had a normal weight prior to becoming pregnant, belong to an ethnic group with a low incidence of diabetes, have no first-degree relatives who have diabetes, have no history of impaired glucose tolerance, and have not had poor obstetric outcomes are considered to be at low risk.[13] The problems in establishing the standard reference intervals for GDM diagnosis have led to controversy on the selection criteria for the diagnosis. Because GDM is influenced by genetics, ethnicity, and socioeconomic and societal variables, standardizing worldwide standards is a challenging task.[13]

Women with risk factors, such as obesity with a BMI of ≥30 Kg/m2, history of gestational diabetes in a prior pregnancy, impaired glucose metabolism, hemoglobin A1C of ≥5.7%, first-degree relative with diabetes mellitus, high-risk ethnicity, history of polycystic ovarian syndrome, pre-existing hypertension or cardiovascular disease, or a prior large baby ≥4000 g, should receive early glucose screening at their first prenatal visit. Early screening aids in detecting people with pre-pregnancy type II diabetes mellitus. Women who have a normal glucose screen in early pregnancy will have the test redone at 24-28 weeks gestation.[9]

Plasma glucose levels were obtained after a fast, followed by a glucose load. The table shows the usual levels. According to the IADPSG, the Canada Diabetes Association, and the NICE standards, GDM is diagnosed when one or more plasma glucose levels exceed the normal range. According to ACOG standards, patients with a positive 1-hour glucose screen are given a 3-hour test, and if two or more readings are high above normal, GDM is diagnosed.[9]

Various complications can occur due to GDM, such as an increased risk of spontaneous abortion, fetal anomalies, preeclampsia, fetal hyperinsulinemia causing neonatal hypoglycemia, hyperbilirubinemia, and respiratory distress syndrome postpartum, fetal hyperglycemia leading to macrosomia which can cause preterm delivery, caesarean delivery, shoulder dystocia, brachial plexus injury and fracture, and perinatal asphyxia which is associated with intrauterine fetal death (IUFD), polycythemia, and hyperbilirubinemia.[10,14,15] Risk of cardiac malformations in the offspring increase 30% more than normoglycemia mothers.[15]GDM patients also have a 50% risk of acquiring into type 2 diabetes mellitus (DM) within 5-10 years after giving birth.[7]

The target glucose for fasting plasma is >95 mg/dL, 1-hour postprandial <140 mg/dL, and 2-hour postprandial <120 mg/dL, with the target HbA1C is <6% without significant hypoglycemia, but <7% is acceptable to prevent hypoglycemia if necessary.[16]Several approach can be used to treat GDM, which is divided into lifestyle intervention such as nutritional therapy, weight management, and exercise, and pharmacological intervention.[4,16]After having diagnosed, treatment starts with nutrition therapy according to the Dietary Reference Intakes (DRI) with a minimum of 175 g of carbohydrate, 71 g of protein, and 28 g of fiber. This intake needs to be distributed into 3 meals and 2-4 snacks in a day.[4] Women need to have an intake of 1,800-2,500 kcal every day. Women with normal body mass index (BMI, 18.5-24.9 kg/m^2) need 30kcal/kg/day, overweight (BMI, 25.0-29.9 kg/m^2) and obese (BMI, 30.0-39.9 kg/m^2) need 22-25 kcal/kg/day. Women with BMI >40 kg/m^2 need 12-14 kcal/kg/day and BMI <18.5 kg/m^2 need 35-40 kcal/kg/day.[17] Exercise depends on the indications and contraindications. Safe activities to start and continue are walking, swimming, cycling, selected pilates, and other low intensity fitness exercises. Several exercises need the approval from the obstetrician to continue such as yoga, running, tennis, badminton, and strength exercises.[3]

When 1-2 weeks of lifestyle intervention does not affect blood glucose levels to reach target, pharmacological treatment is given.[4]Orally administered drugs (OAD) are usually given only when the patient denied insulin therapy or the drugs are unavailable. The safest choice of drugs for pregnant women are metformin and glyburide due to the unlikeliness to be teratogenic, but complications for IUFD, and neonatal complications such as hypoglycemia, macrosomia, and fetal growth restriction (FGR) is at a higher risk.[3]Insulin therapy become the preferred approach for GDM if glucose levels are still elevated after nutritional therapy.[15]There are multiple types of insulin that can be chosen based on the necessity, convenience, administration, and disadvantages. Hence, this study aims to summarize the treatment for GDM using insulin to produce the best option to effectively treat GDM.

METHOD

The study uses an analysis of data available in literatures based on reviews, original articles, and meta-analyses published in English in the last 5 years. A literature search is conducted using NCBI, PubMed, and Science Direct databases that includes keywords such as "gestational diabetes", "insulin therapy", "types of insulin", and "management", that were used alone or in combination.

RESULTS AND DISCUSSION

Insulin therapy become the safest option globally for GDM which have an immediate effect on maternal blood glucose levels. Aside from OAD, insulin do not cross the placenta and not associated with any fetal complications that may occur.[18]There are several types of insulin: human insulin, rapid-acting insulin analogs, intermediate insulin, and basal analogs.[4]

1. Human insulin
    a. Regular insulin
    Regular insulin is similar to human insulin, available in two dose, U-100 and U-500. It is used after meal to decrease postprandial hyperglycemia. The onset is around 30 minutes (10-75 minutes) with the effect reaching its peak in 3 hours (2.5-5 hours) and ends after 8 hours or up to 24 hours using U-500. It is categorized as B class drugs for pregnancy by FDA.[4]
    b. Human insulin inhalation (nasal insulin)
    Nasal insulin is equal to insulin lispro unit-for-unit. The onset is 15 minutes with peak action around 50 minutes and effective up to 2 hours. This is a pregnancy category C drugs which is not suitable for patients with chronic lung disease due to the risk of bronchospasms.[4]

2. Rapid-acting insulin analogs
   a. Insulin as part
      Insulin as part is made from a type of yeast called Saccharomyces cereviseae. This type of insulin can be injected subcutaneously or using an insulin pump 5-10 minutes before meal. Peak action is 40-50 minutes with duration 3-5 hours. The risk for hypoglycemia and any adverse effect on the pregnancy or fetal/neonatal is lower than using regular insulin.[4]
   b. Insulin lispro
      Insulin lispro is produced in Escherichia coli cultures. U-100 and U-200 doses are available with onset time is 10-15 minutes. This insulin peaks in 30-90 minutes and last for 3-4 hours. It is administered using pumps or pens. This is a category B drugs that have not shown any adverse effects on pregnancy or fetal/neonatal health.[4]
   c. Insulin glulisine
      Insulin glulisine is a recombinant insulin acquired using Eschericia coli. Onset time is 10-15 minutes, peaking in 55 minutes, and works for 4-5 hours. This insulin needs to be administered with the approved pumps. This is an FDA pregnancy category C and potential benefit needs to be more significant than the potential risk.[4]
3. Intermediate insulin
   Insulin isophane (NPH) is an intermediate-acting insulin which is produced in *Eschericia coli*. It is a liquid suspensu=ion similar to to human insulin that starts working in maximum 2 hours and peaking in around 4 hours. The effect lasts 10-20 hours and is categorized a B class drugs.[4]
4. Basal analogs
   a. Insulin detemir
      Insulin detemir is a long-acting analog produced in Saccharomyces cerevisae. The available dose is U-100 with onset 1-2 hours and lasting for 24 hours without peak time. Hypoglycemia founded less when using insulin detemir compared to NPH.[4]
   b. Insulin glargine
      Insulin glargine is produce in Escherichia coli. U-100 onset time is 1-2 hours and slowly releasing for over 24 hours without peaking. The U-300 is not bioequivalent to U-100 and peaking after 6 hours and starts to decline after 16-36 hours.[4]
   c. Insulin degludec
      The U-100 and U-200 is bioequivalent with the onset time nearing 1 hour without peaking and dosed once daily given at any time of the day. The use of pregnancy have not been done.[4]

The regimen chosen to treat hyperglycemia varies but the most efficient and flexible way is by multiple daily injection (MDI). Basal insulin with the dose of 0.2 units/kg/day is chosen if fasting blood glucose levels surpass normal range, while rapid-acting or regular insulin can be used if hyperglycemia happens after meal with the dose of 1 unit every 10-15 grams of carbohydrate, administered before meal. When both fasting and postprandial glucose levels are elevated, MDI is chosen with the combination of 3 mealtime insulin and basal insulin with the total daily insulin needed for the first trimester is 0.7 units/kg/day, second semester is 0.8 units/kg/day, and the third semester is 0.9-1.0 units/kg/day. Dose can double if patient is diagnosed with diabetes before pregnancy.[4]

CONCLUSION

The best treatment for GDM is insulin therapy which have little to no complications to the pregnancy and fetal/neonatal. An MDI regimen is mostly selected using the combination of mealtime and postprandial insulin with the total of daily dose increase 0.1 unit/kg/day for each trimester starting from 0.7 units/kg/day and divided into 3 mealtime insulin and 1 basal insulin. However, if blood glucose levels are only elevated after fasting, basal insulin with dose of 0.2 units/kg/day can be given, or if hyperglycemia occurs after meal, 1 unit/10-15 g carbohydrate is administered. As for pregestational diabetes patients, the regimen dosage is doubled.

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