Insulin Treatment for Gestational Diabetes Mellitus

I Gde Sastra Winata,[1] Prayascita Mahendrata,[2] Made Yudha Ganesa Wikantyas Widia,[1] William Alexander Setiawan,[1] Jessica Nathalia[1]

[1]Obstetric and Gynecology Department, Faculty of Medicine, Udayana University, Bali, Indonesia

[2]Obstetric and Gynecology Department, Bali Mandara General Hospital, Indonesia

Correspondence: I Gde Sastra Winata, Email: sastra@unud.ac.id

Abstract

Introduction: Gestational diabetes is one of the most common pathologies in pregnancy that can potentially cause other complications, both to the mother and the fetus. This condition is considered a global health problem, with Asia having the highest prevalence.

Methods: This article is a literature review of publications from the past five years (2019–2024) obtained from the NCBI, PubMed, and Science Direct databases. The keywords used include "gestational diabetes," "insulin therapy," "types of insulin," dan "management".

Results: Insulin remains the gold standard therapy for managing GDM when lifestyle interventions over 1–2 weeks fail to achieve glycemic targets. Various types of insulin, such as human insulin, rapid-acting analogs (lispro, aspart), intermediate-acting insulin (NPH), and basal analogs (detemir, glargine), are considered safe and effective for use during pregnancy

Discussion: The main advantage of insulin is that it does not cross the placenta, thereby avoiding teratogenic risks. Some insulin analogs, such as lispro and detemir, have the advantage of reducing the risk of maternal hypoglycemia and providing more stable glycemic control.

Conclusion: Insulin is the only therapy that does not cross the placenta, and most types do not affect pregnancy and fetuses or neonates.

Keywords: diabetes gestational; insulin; treatment

Pengobatan Insulin untuk Diabetes Mellitus Gestasional

Abstrak

Pendahuluan: Diabetes gestasional merupakan salah satu patologi yang paling umum terjadi pada kehamilan. Penyakit ini berpotensi menimbulkan komplikasi lain, baik pada ibu maupun janin. Kondisi ini dianggap sebagai masalah kesehatan global dan di Asia memiliki prevalensi tertinggi.

Metode: Artikel ini merupakan tinjauan literatur dari publikasi dalam lima tahun terakhir (2019–2024) yang diperoleh dari basis data NCBI, PubMed, dan Science Direct. Kata kunci yang digunakan meliputi "gestational diabetes," "insulin therapy," "types of insulin," dan "management".

Hasil: Hasil penelitian menunjukkan bahwa insulin tetap menjadi terapi standar emas dalam penatalaksanaan GDM apabila intervensi gaya hidup selama 1 – 2 minggu tidak mampu mencapai target glikemik. Berbagai jenis insulin seperti insulin manusia, analog kerja cepat (lispro, aspart), insulin intermediet (NPH), dan analog basal (detemir, glargine) dinilai aman dan efektif digunakan selama kehamilan.

Diskusi: Keuntungan utama insulin adalah tidak melewati plasenta sehingga menghindari risiko teratogenik. Beberapa jenis insulin analog seperti lispro dan detemir memiliki keunggulan berupa penurunan risiko hipoglikemia maternal dan kontrol glikemik yang lebih stabil.

Kesimpulan: Insulin merupakan satu-satunya terapi yang tidak melewati plasenta dan sebagian besar jenis insulin tidak memiliki efek pada kehamilan dan janin atau neonatus.

Kata kunci: diabetes gestasional; insulin; tatalaksana

Introduction

Gestational diabetes mellitus (GDM) is defined as a glucose intolerance that is first recognized during the 24th week of pregnancy, excluding patients who meet the criteria for type 2 diabetes mellitus and whose blood glucose levels return 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 a global health problem, with 7% of pregnancies being diagnosed with GDM.1 A prevalence of 14.7% worldwide, representing more than 20 million births annually.3, 5 Asians, in particular, have a high prevalence, ranging from 8.8% to 20% in the Middle East, 9.6% to 18.3% in Southeast Asia, and 4.5% to 20.3% in the Western Pacific.6 In Indonesia, 1.9-3.6% of pregnant women suffer from GDM.[7]

When 1-2 weeks of lifestyle intervention does not affect blood glucose levels to reach the target, pharmacological treatment is given.[4] Orally administered drugs (OADs) are usually given only when the patient has denied insulin therapy or the drugs are unavailable. The safest choices of medications for pregnant women are metformin and glyburide due to their being unlikely to be teratogenic. Still, IUFD and neonatal complications such as hypoglycemia, macrosomia, and fetal growth restriction (FGR) are at a higher risk.[3]. Insulin therapy becomes the preferred approach for GDM if glucose levels are still elevated after nutritional treatment.[8] Multiple types of insulin can be chosen based on necessity, convenience, administration, and disadvantages. The purpose of this review is to review and analyze various types of insulin therapy used in the management of gestational diabetes, as well as to evaluate the effectiveness and safety for pregnant women and fetuses. The literature review was performed based on the literature published within the last five years (2019 – 2024).

Method

The study employs an analysis of data available in the literature, based on reviews, original articles, and meta-analyses published in English over the last five years (2019-2024). A literature search is conducted using the NCBI, PubMed, and ScienceDirect databases. The keywords used in the literature search included "gestational diabetes," "insulin therapy," "types of insulin," and "management". The inclusion criteria for this study are articles written in English, journals available in online versions, and research journals or review articles published within the last five years, from 2019 to 2024. The exclusion criteria include journals that do not contain information related to the main keywords, articles with limited access (not full text). After screening, a total of 44 scientific articles were identified. Of these, 10 articles met the inclusion criteria and were selected as primary references for writing this review.

Results

Based on the analysis of recent literature, insulin therapy remains the gold standard treatment for gestational diabetes mellitus (GDM), effectively controlling maternal blood glucose levels while avoiding transplacental drug transfer and associated fetal risks.[4] Various types of insulin, including human insulin, rapid-acting insulin

analogues, intermediate insulin, and basal analogues, have been evaluated for their safety and efficacy during pregnancy.[4]

The findings indicate that while lifestyle modifications, including dietary adjustments and physical activity, remain the first-line management strategy, insulin therapy is essential when target glucose levels are not achieved within 1– 2 weeks of intervention. Among the insulin types analysed, rapid-acting insulin analogues, such as insulin aspart and insulin lispro, are associated with a lower risk of maternal hypoglycemia compared to regular human insulin. Meanwhile, basal insulin analogues, particularly insulin detemir, provide sustained glycemic control with fewer episodes of nocturnal hypoglycemia [4, 9–11]

Discussion

Aside from OAD, insulin does not cross the placenta and is not associated with any fetal complications that may occur.[12] Insulin therapy during pregnancy must be individualised and dynamically adjusted to meet the changing physiological demands of gestation. Intensive insulin regimens, including basal-bolus therapy or continuous subcutaneous insulin infusion (CSII), are recommended to achieve and maintain target glycemic levels both preconception and throughout pregnancy. Women using CSII should be counselled regarding the potential risk of diabetic ketoacidosis (DKA) in the event of pump malfunction; however, current evidence does not suggest a higher incidence of DKA with CSII compared to multiple daily injections (MDI).[13, 14]

Rapid-acting insulin analogues, such as insulin aspart and insulin lispro, are considered safe for use during pregnancy. These agents have demonstrated benefits in improving postprandial glycemic control and reducing the frequency of maternal hypoglycemia relative to regular human insulin. Although placental transfer of insulin aspart has not been studied, insulin lispro has been shown not to cross the placenta at typical therapeutic doses (<50 units), similar to human insulin.[13, 14]

A meta-analysis of observational studies involving 1,561 women with pre-existing diabetes and gestational diabetes mellitus (GDM) found that insulin lispro was associated with a lower risk of severe maternal hypoglycemia and neonatal jaundice, albeit with an increased incidence of large-for-gestational-age (LGA) infants. In a randomised controlled trial (RCT) of 322 women with type 1 diabetes, insulin aspart was associated with improved postprandial glucose control and a trend toward fewer episodes of severe hypoglycemia, resulting in overall glycemic control comparable to that achieved with regular insulin. A smaller, underpowered trial reported no significant difference in perinatal outcomes between insulin aspart and human insulin.[14, 15]

A meta-analysis of RCTs involving 1,143 women with GDM or pre-existing diabetes comparing insulin aspart (including premixed biphasic formulations) with regular insulin reported similar rates of cesarean delivery and macrosomia. Additionally, a case series of 303 pregnancies exposed to insulin glulisine did not identify any consistent pattern of congenital anomalies. At present, there are no published data on the safety or efficacy of faster-acting insulin aspart during pregnancy.[15 – 17]

Long-acting insulin analogues, including insulin glargine and insulin detemir, appear to be safe and effective in pregnancy, with maternal and fetal outcomes comparable to those observed with neutral protamine Hagedorn (NPH) insulin. Neither glargine nor detemir crosses the placenta at therapeutic doses, though glargine may cross at supratherapeutic levels. Two RCTs evaluating insulin detemir versus NPH in women with type 1 diabetes demonstrated

Table 1. Comparison of Insulin Types Used in Gestational Diabetes Management.[4, 13 – 17]

Insulin Type	Onset	Duration	FDA Pregnancy Category	Advantages	Disadvantages
Regular Human Insulin (U-100 / U-500)	30 mins (10–75 mins)	8 hrs (up to 24 hrs with U-500)	B	Well-studied; safe in pregnancy	Slower onset; higher risk of postprandial hyperglycemia
Inhaled Human Insulin	15 mins	~2 hrs	C	Rapid onset; convenient	Not for patients with lung disease; limited safety data in pregnancy
Insulin Aspart	5–10 mins	3–5 hrs	B	Lower risk of maternal hypoglycemia; good postprandial control	Limited data on placental transfer
Insulin Lispro	10–15 mins	3–4 hrs	B	Safe; well-studied in pregnancy; fast action	Potential for LGA babies in some studies
Insulin Glulisine	10–15 mins	4–5 hrs	C	Rapid absorption	Less evidence in pregnancy; use only if benefits outweigh risks
NPH (Insulin Isophane)	≤2 hrs	10–20 hrs	B	Intermediate-acting; well-known	Higher risk of nocturnal hypoglycemia compared to analogs
Insulin Detemir	1–2 hrs	~24 hrs (no peak)	B	Consistent glycemic control; reduced nocturnal hypoglycemia	Higher cost than NPH
Insulin Glargine (U-100)	1–2 hrs	>24 hrs (no peak)	C	Stable basal coverage	Limited RCT data in pregnancy; may cross placenta at high doses
Insulin Glargine (U-300)	~6 hrs	16–36 hrs	C	Prolonged effect; fewer injections	No data available for pregnancy use
Insulin Degludec (U-100/U-200)	~1 hr	>24 hrs (no peak)	C	Flexible dosing; ultra-long action	Not studied in pregnant women

lower fasting blood glucose levels with detemir, with similar A1C values, maternal hypoglycemia rates, and perinatal outcomes. One of these trials also reported a reduced incidence of maternal hypoglycemia with detemir. Although evidence for insulin glargine is limited to cohort and case-control studies, a meta-analysis of cohort data found no significant differences in maternal or fetal outcomes compared to NPH insulin, and no adverse safety signals have been identified. Currently, there are no available data on the use of glargine U-300, lispro U-200, insulin degludec (U-100 or U-200), or biosimilar glargine preparations during pregnancy.[14 – 17]

The 2023 guideline from the American College of Obstetricians and Gynecologists (ACOG) maintains insulin as the preferred pharmacological treatment for gestational diabetes mellitus (GDM) when lifestyle and dietary modifications are insufficient to achieve glycemic targets within 1–2 weeks. ACOG supports the use of insulin due to its efficacy and minimal transplacental transfer, making it a safe option during pregnancy.[18]

According to ACOG 2023, human insulin (NPH and regular) and certain insulin analogs such as insulin lispro, insulin aspart, and insulin detemir are considered safe and effective during pregnancy. These recommendations are based on studies demonstrating improved glycemic control and reduced maternal hypoglycemia, with no significant risk to the fetus.[18-20]

Newer insulin analogs, particularly rapid-acting (lispro, aspart) and long-acting analogs (detemir), offer several clinical benefits, including improved postprandial glucose control due to a faster onset of action, a lower incidence of maternal hypoglycemia, especially nocturnal episodes, more stable glycemic profiles, and a reduced risk of glucose fluctuations.[19 –21]

Despite the advantages, ongoing debates persist regarding the use of ultra-long-acting and newer analogs, such as insulin glargine U-300, insulin degludec, and biosimilar glargine preparations, during pregnancy. These agents are not routinely recommended by ACOG 2023 due to limited safety data in pregnant populations, concerns about placental transfer at supratherapeutic doses (as noted in glargine), a lack of high-quality randomized trials evaluating maternal and fetal outcomes, and cost and accessibility issues, especially in low-resource settings. Insulin degludec, although promising due to its ultra-long duration and flexible dosing, currently lacks sufficient evidence to support its use in pregnant women and is not endorsed by current guidelines.[22 – 24]

To summarize, insulin lispro, insulin aspart and insulin detemir are recommended by multiple guidelines as safe for use during pregnancy for GDM.[13,14] The regimen chosen to treat hyperglycemia varies, but the most efficient and flexible way is by multiple daily injection (MDI). Basal insulin, with a dose of 0.2 units/kg/day, is chosen if fasting blood glucose levels exceed the normal range. Alternatively, rapid-acting or regular insulin can be used if hyperglycemia occurs after a meal, with a dose of 1 unit every 10-15 grams of carbohydrate, administered before the meal. When both fasting and postprandial glucose levels are elevated, MDI is chosen, combining 3 mealtime insulin and basal insulin, with a total daily insulin dose of 0.7 units/kg/day in the first trimester and 0.8 units/kg/day in the second trimester. The third semester is 0.9-1.0 units/kg/day. The dose can double if the patient is diagnosed with diabetes before pregnancy.[4]

Conclusion

Insulin remains the preferred pharmacologic treatment for gestational diabetes mellitus (GDM) when lifestyle modifications are insufficient. Established insulin analogs, such as aspart, lispro, and detemir, offer improved glycemic control and are generally considered

safe during pregnancy. While newer analogs, such as glargine U-300 and degludec, show potential benefits, current evidence is limited, and their routine use during pregnancy is not yet supported. Treatment should be individualized, considering clinical response, safety, and availability.

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