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Insulin Therapy in Gestational Diabetes

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Abstract

The prevalence of gestational diabetes risen in several populations during the past 20 years, and increased direct and indirect healthcare costs, including those for insulin treatment. Establishing the optimal treatment and initiation momentum are critical to achieve glycemic control and minimize the impact on fetal development and perinatal complications. Insulin is the only therapy that does not cross the placenta, and some of its types were proved to be safe in pregnancy. Intrapartum management is based on intravenous insulin administration, and standard protocols should be implemented in every center. Postpartum management requires special attention, as insulin necessary has a fast decline exposing mothers to hypoglycemia.

Keywords: gestational diabetes, insulin therapy, macrosomia, neonatal hypoglycemia

1. Introduction

Gestational diabetes (GD) is one of the most common pathologies in pregnancy. Gestational diabetes has been defined as any degree of glucose intolerance with onset or first recognition during pregnancy [1]. In pregnancy, there are multiple hormonal changes, including hyperinsulinemia and an insulin-resistant state; thus the pancreatic beta cell function becomes insufficient to meet the body's reasonable needs, and insulin must be injected.

There is also the possibility that hyperglycemia was present before the pregnancy; therefore International Association of Diabetes and Pregnancy Study Groups (IADPSG) defined the pregnancy hyperglycemia as either 'overt diabetes' or 'gestational diabetes mellitus' (GDM) [2].

Considering the ascending trend of type 2 diabetes mellitus and obesity from the last decades, GD has intuitively the same tendency [3, 4]. The prevalence of GD is estimated at approximately 135,000 cases per year in the US [5], representing on average 3–8% of all pregnancies [6]. It is estimated that the prevalence of GD has increased by 10–100% in several racial groups during the past 20 years, increasing direct and indirect healthcare costs [5].

The goal of treatment for women with GD (recommended by both American Diabetes Association-ADA, and the American College of Obstetricians and Gynecologists-ACOG) is a fasting plasma glucose level <95 mg/dl, a 1-hour post-prandial glucose level of less than 140 mg/dl and a 2-hour post-prandial glucose level of less than 120 mg/dl, whereas for the HbA1c the target is <6–6.5% (42–48 mmol/mol); lower HbA1c—6% (42 mmol/mol) is optimal if it can be achieved without significant

hypoglycemia; also, the target may be relaxed to 7% (53 mmol/mol) in order to prevent hypoglycemia [7, 8].

2. Lifestyle intervention

After diagnosis GD, to reach the goals for plasma glucose levels, the first step is the initiation of a lifestyle intervention program (including medical nutrition therapy—MNT and physical activity—PA).

MNT is the cornerstone of the GDM treatment. MNT alone can assure glycemic targets in 80–90% of GDM patients [9]. Maternal height and weight are key factors for the medical nutrition therapy, providing adequate calories and nutrients for both maternal and fetal nutrition, maintaining glycemic targets and the absence of ketones with appropriate weight gain [10–12]. For a GDM mother with a normal body mass index (BMI) of 18.5–24.9 kg/m², the number of adequate calories is about 30 kcal/kg [9]. Nevertheless, since more than 60% of women diagnosed with GDM are overweight or obese, a caloric restriction is needed. The ADA states that no research identifies a specific optimal calorie intake for women with GDM and that the calorie needs are no different from those of pregnant women without GDM [7]. Therefore, ADA issued only general recommendations (following the dietary reference intakes) for 175 g of carbohydrate, 71 g of protein, 28 g of fiber, emphasizing the importance of the amount and type of carbohydrate with significant impact concerning the glucose levels, especially postprandial glucose peak [7]. ADA recommends individualized nutrition plan developed by a registered dietitian familiar with the management of GDM [7]. The National Institute for Health and Care Excellence (NICE) guidelines recommend a healthy diet, emphasizing the importance of low glycemic index foods (that should replace those with a high glycemic index) for GDM women; also there is the recommendation for a dietitian when GDM is present [13].

The carbohydrate intake should be reduced to 33–45% of the total calories, and distributed over 3 meals, and 2–4 snacks/day, thus reducing postprandial glucose peak [8, 14], while as the rest of the calories should be divided between protein (20%) and lipids (40%) [15].

Excessive weight gain during pregnancy should be avoided for GDM women [16]. The weight gain during pregnancy depends on pre-pregnancy BMI:

- 12.5–18 kg of weight gain for underweight women (BMI <18.5 kg/m²);
- 11.5–16 kg for normal weight (BMI 18.5–24.9 kg/m²);
- 7–11.5 kg for overweight (BMI 25–29.9 kg/m²)
- 5–9 kg for obese (BMI ≥30.0 kg/m²) [17]

Physical activity improves glycemic control in GDM women. The generally accepted recommendation is daily moderate-intensity regular exercise (walking 30 minutes/day or more—if no medical contraindications) improves blood glucose control [13, 14].

3. Pharmacological treatment

Pharmacological treatment is recommended when lifestyle intervention does not reduce hyperglycemia to reach the glycemic target. There is no international

consensus on when to start pharmacological treatment of GDM [18]. The Canadian Diabetes Association (CDA) and NICE guidelines, both recommend beginning pharmacological treatment if glycemic control is not achieved after 1–2 weeks of lifestyle intervention [13, 19].

Oral antidiabetic medication has been described in a previous chapter. The authors want to resume the most important clinical implications and the comparisons with insulin treatment.

3.1 Metformin

The use of metformin in GDM after the glycemic target is not reached with lifestyle intervention is recommended by the NICE guidelines [13]. Metformin is classified as a category B drug, which implies that there is no evidence of animal, or fetal toxicity or teratogenicity. In general, metformin appears to be a safe alternative to insulin for the GDM treatment, but it crosses the placenta, and it may be present in a higher concentration in the fetal circulation than in the maternal circulation [19]. Studies were performed for the assessment of metformin exposure in-utero. There is no evidence that the metformin is affecting the fetus with regards to an early motor, linguistic, social, [20], metabolic [20, 21], and neurodevelopmental [22, 23] outcomes, but long-term follow up studies are needed. The metformin was associated with a lower risk of neonatal hypoglycemia and less maternal weight gain than insulin in two systematic reviews [24, 25]. Almost half of the patients with GDM who were initially treated with metformin needed insulin to achieve acceptable glucose control [26]. Metformin remains an option as a second line treatment in GDM women who refuse insulin treatment or who are unable to administer insulin safely.

3.2 Glyburide

Glyburide (glibenclamide) was associated with increased birth weight, macrosomia and neonatal hypoglycemia compared with insulin [20, 25], and similar to metformin, crosses the placenta [27]. Glyburide therapy during pregnancy is not recommended as first- or second-line treatment, but it may be used as third-line treatment if insulin is refused, and metformin is either refused or insufficient to reach targeted glycemic control [19].

There is no human data for the use of any other antihyperglycemic medication in the treatment of GDM (DPP-4 inhibitors, GLP-1 receptor agonists or SGLT2 inhibitors) [19]. Patients treated with oral therapy should be informed that they cross the placenta. No adverse effects on the fetus have been demonstrated; long-term studies are lacking [7].

3.3 Insulin therapy

Insulin is the first-line antihyperglycemic medication recommended for treatment of GDM [7, 19]. None of the currently available insulin preparations has been demonstrated to cross the placenta [7]. If glycemic control is not achieved after 1–2 weeks of lifestyle intervention, insulin treatment should be initiated [19]. Insulin remains the gold standard treatment for GDM women that do not reach glycemic targets with lifestyle intervention, as recommended by several guidelines (see **Table 1** below). Insulin use reduces fetal and maternal morbidity [28, 29].

International Federation of Gynecology and Obstetrics (FIGO), 2015	<ul style="list-style-type: none">- Oral therapy failure or- One of the risk factors:<ul style="list-style-type: none">• Diagnosing diabetes before 20 weeks of gestation• Oral therapy for more than 30 weeks• Fasting plasma blood glucose above 110 mg/dl• 1-hour postprandial glycemia above 140 mg/dl• Weight gain over 12 kilograms during pregnancy
Canadian Diabetes Association (CDA), 2018	If glycemic control is not achieved in 2 weeks after the initiation of medical, nutritional intervention
American Diabetes Association (ADA), 2018	First line therapy if glycemic control is not achieved after diet intervention
American College of Obstetricians and Gynecologists (ACOG), 2018	First line therapy if glycemic control is not achieved after diet intervention

Table 1.
Insulin initiation recommendations.

3.3.1 *Types of insulin*

3.3.1.1 *Human insulin*

3.3.1.1.1 *Regular insulin*

Regular insulin (U-100, U-500) is identical to human insulin, and it is used as meal-time insulin to cover postprandial hyperglycemia. Its time to onset is about 30 minutes (10–75 minutes), the peak effect is in 3 hours (2.5–5 hours), and the effect ends at about 8 hours (up to 24 hours for U500). The FDA pregnancy category is B [30].

3.3.1.1.2 *Human insulin inhalation (nasal insulin)*

Human insulin inhalation (nasal insulin) is equivalent unit-for-unit to insulin lispro. Its onset is 15 minutes, and its peak action time is ~50 minutes. Duration of action is about 2 hours. Inhaled human insulin carries a boxed warning for bronchospasms in patients with chronic lung disease. It is a pregnancy category C drug [30].

3.3.1.2 *Rapid-acting insulin analogs*

Another analog of human insulin is insulin aspart produced from *Saccharomyces cerevisiae*, a type of yeast. Aspart should be taken 5–10 minutes before a meal. It can be used like for multiple subcutaneous injections or in insulin pumps. Its peak action time is 40–50 minutes, and its duration of action is 3–5 hours. Insulin aspart produce less hypoglycemia than the regular insulin [31]. The FDA pregnancy category is B and can be used in pregnancy. Data from two clinical trials (349 exposed pregnancies) do not indicate any adverse effect on pregnancy or fetal/neonatal health compared with human insulin [30].

3.3.1.2.1 *Insulin aspart*

Insulin aspart was introduced on the market with nicotinamide and L-arginine hydrochloride as excipients to enhance its absorption. Although the active molecule is identical, there are no available data for its use in pregnancy and its excretion in human milk [30].

3.3.1.2.2 *Insulin lispro*

Insulin lispro (U-100 and U-200) is an analog produced in *Escherichia coli* cultures. Its onset of action is 10–15 minutes. The peak is at 30–90 minutes, and its duration of action is 3–4 hours. Also, it can be used in insulin pumps or pens. The U-100 and U-200 formulations have the same bioequivalence and pharmacokinetics. The FDA pregnancy category is B and can be used in pregnancy. The data from a large number of exposed pregnancies do not indicate any adverse effect on pregnancy or fetal/neonatal health [30].

3.3.1.2.3 *Insulin glulisine*

Insulin glulisine is a recombinant insulin. It is obtained using *Escherichia coli*. It works fast nearly in 10–15 minutes. Its peak installs in 55 minutes, and its full duration is 4–5 hours. Although it can be used in some insulin pumps, it is not approved for all pump brands. The FDA pregnancy category is C. In this case, the vigilance should be given when prescribing glulisine to pregnant women, and the drug should only be used if the potential benefit justifies the potential risk to the fetus. There are limited data (less than 300 pregnancy outcomes) from the use of insulin glulisine in pregnant women [30].

3.3.1.3 *Intermediate insulin*

3.3.1.3.1 *Insulin isophane*

Insulin isophane (NPH) is an intermediate-acting insulin. It is also produced in *Escherichia coli*. It is similar to human insulin and is presented in a liquid suspension. Its onset of action is maximum 2 hours, with an average peak of 4 hours. NPH full duration of action is 10–20 hours. No restrictions on use in gestational diabetes or pregnancy; do not cross the placental barrier. The FDA pregnancy category is B [30].

3.3.1.4 *Basal analogs*

3.3.1.4.1 *Insulin detemir*

Insulin detemir (U-100) is a long-acting analog produced in *Saccharomyces cerevisiae*. Detemir insulin lacks a defined peak and lasts for up to 24 hours, and time to onset of action can be 1–2 hours. The detemir insulin has less incidence of hypoglycemia compared to NPH regimen in pregnant women [32]. The FDA pregnancy category is B; considered during pregnancy. The potential benefit must be considered against the possible increased risk of adverse pregnancy outcomes. One clinical trial suggests a possible increased risk of serious adverse maternal outcomes compared with isophane insulin and data from an additional 250 outcomes from pregnant women exposed to insulin detemir suggest no maternal or fetal/neonatal toxicity [30].

3.3.1.4.2 *Insulin glargine*

Insulin glargine (U-100) is a long-acting analog produced in *Escherichia coli*. The acidic solution is neutralized in subcutaneous tissue, and micro precipitates are formed. These micro precipitates slowly release glargine over 24 hours. Its onset of action is 1–2 hours, its duration of action are 24 hours and has no peak. The FDA

pregnancy category was previously C, no human pregnancy data. May be considered during pregnancy, if necessary, but we do not have clinical data on exposed pregnancies from controlled clinical studies available. The data from pregnant women (between 300 and 1000 pregnancy outcomes) indicate no adverse effects on pregnancy, nor malformations or feto-neonatal toxicity [30].

3.3.1.4.3 Insulin glargine

Insulin glargine (U-300) is a long-acting insulin. It is not bioequivalent to glargine U-100, but it had the same structure and was approved in February 2015. Glargine U-300 is produced in *Escherichia coli*. Its peak action develops over 6 hours and continues for an entire 24 hours. The serum concentrations decline after 16–36 hours. It is dosed once daily. There is no clinical experience until now with the use of insulin glargine (U-300) in pregnant women [30].

3.3.1.4.4 Insulin degludec

Insulin degludec U-100 and U-200 are considered bioequivalent. The insulin degludec's mode of slow absorption and prolonged action is based on the formation of soluble multi-hexamers. Insulin degludec onset of action is nearly 1 hour and has no peak. It is dosed once daily. It can be dosed at any time of the day because of its long duration of action. There is no clinical experience in pregnant women [30].

3.3.2 Insulin regimens

There are many insulin regimens proposed for treating hyperglycemia, but the multiple daily injections (MDI) is by far the most efficient and the most flexible [33].

The insulin regimen should be chosen based on the blood glucose profile. Therefore, if fasting glycaemia is higher than 90–95 mg/dl, basal insulin should be initiated. It can be a long-acting insulin analog or neutral protamine Hagedorn. The basal insulin dose can be calculated according to the weight: 0.2 units/kg/day.

If the hyperglycemia follows a meal, then rapid-acting insulin or regular insulin should be initiated before that meal (begin with 1 u of insulin for 10–15 g of carbohydrates).

Sometimes both fasting and postprandial glycaemia are elevated, thereby needing MDI: 3 mealtime insulin and basal insulin. The total daily insulin requirement during the first trimester, is 0.7 units/kg/day, while in the second trimester it is 0.8 units/kg/day, and in the third trimester, it is 0.9–1.0 units/kg/day. This does not necessarily fit all pregnancies. Usually, in pregestational diabetes, the total insulin dose is up to twice higher than in GDM.

In the case of morbid obesity, the initial doses of insulin can be increased to 1.5–2.0 units/kg to overcome the combined IR of pregnancy and obesity [9].

Usually, the calculated total daily dose of insulin should be divided in two as for type 1 and type 2 diabetes: 50% as basal insulin at bedtime, and 50% divided between 3 meals and given as rapid-acting, or regular insulin before meals.

The doses of insulin have to be continuously optimized, so the self-monitoring blood glucose is essential.

Rapid-acting insulin analogs are preferred over regular insulin in pregnancy because there is a lower risk of hypoglycemia, and because they provide a better postprandial blood glucose control [29, 33].

3.3.3 Insulin initiation

Insulin initiation is synthesized in **Table 1**.

3.4 Glycemic targets and control

Blood glucose control is important in gestational diabetes because it confers the future mother a sense of disease control and validation that diet and treatment are doing their effect as the glycemic control improves, the risk of maternal and fetal complications decreases, a principle that was demonstrated by HAPO study results [34]. The results of this landmark study and other seven randomized trials have been included in a Cochrane analysis that compared the treatment of gestational diabetes mellitus (GDM) with standard care. It demonstrated a lower risk of a composite endpoint (death, shoulder dystocia, humerus, clavicle fracture or nerve palsy), and also a lower risk of pre-eclampsia and macrosomia (birth weight over 4000 g or 90th percentile), with no differences between oral and injectable treatment [35].

Thereby, gestational auto monitoring and surveillance by an obstetrician in collaboration with the diabetologist, nutritionist and midwife is essential for achieving glycemic targets during pregnancy, labor and after birth. These targets are synthesized in **Tables 2** and **3**.

3.5 Methods for glucose monitoring

3.5.1 Glycated hemoglobin (HbA1c)

Although glycated hemoglobin values must be interpreted with caution in patients with dilution anemia, iron deficiency anemia or other hematological

5th International Workshop Conference Gestational Diabetes and International Association of Diabetes and Pregnancy Study Group, 2007	Capillary pre-prandial glucose <95 mg/dl (5.3 mmol/l) Capillary 1 hour post-prandial glucose <140 mg/dl (7.8 mmol/l) Capillary 2 hour post-prandial glucose <120 mg/dl (6.7 mmol/l)
FIGO, 2015	Capillary pre-prandial glucose <95 mg/dl (5.3 mmol/l) Capillary 1 hour post-prandial glucose <140 mg/dl (7.8 mmol/l) Capillary 2 hour post-prandial glucose <120 mg/dl (6.7 mmol/l)
CDA, 2018	Capillary pre-prandial glucose <95 mg/dl (5.3 mmol/l) Capillary 1 hour post-prandial glucose <140 mg/dl (7.8 mmol/l) Capillary 2 hour post-prandial glucose <120 mg/dl (6.7 mmol/l)
ADA, 2018	Capillary pre-prandial glucose <95 mg/dl (5.3 mmol/l) Capillary 1 hour post-prandial glucose <140 mg/dl (7.8 mmol/l) Capillary 2 hour post-prandial glucose <120 mg/dl (6.7 mmol/l)

Table 2.
Glycemic targets during pregnancy.

FIGO, 2015	Capillary glucose 72–126 mg/dl (4–7 mmol/l)
ACOG, 2018	Capillary glucose 70–110 mg/dl (3.9–3.1 mmol/l)

Table 3.
Glycemic targets during labor.

pathologies like minor thalassemia [36, 37], it proves to be useful in checking the self-reported date by the pregnant, especially if she is treated with insulin.

Other parameters that could be used for short-term (2–3 weeks) evaluation of blood glucose control is glycated albumin. It is not influenced by iron deficiency, but the values are low in nephrotic syndrome or thyroid disorders that sometimes are present in pregnancy. This marker was studied in GDM, but the cutoff limits are not precisely known with consideration of some population differences [38]. Molecules like fructosamine or 1,5-anhydroglucitol have not proven their utility [39–41].

3.5.2 Self-monitoring of capillary blood glucose (SMBG)

The efficiency of capillary blood testing (8 determinations per day) in pregnant diabetes patients has been demonstrated since the 1980s [42]. Current guidelines [7, 8, 12, 18] mention in general terms the frequency and optimal period (fasting, 1 or 2 hours postprandial) when a test should be done without customizing for treatment, previous glycemic control.

In healthy adult pregnant women, 1-hour glycemia during a glucose challenge test was a better marker for insulin sensibility, being correlated with a fetal abdominal circumference in echography [43]. In Jovanovic and collab study [42], glycemia at 1 hour after food intake in the third trimester was the best predictor for birth weight. Combs et al. used the same 1-hour glycemia to establish the best threshold (130 mg/dl) for which the risk for macrosomia and small for gestational age (SGA) is reduced [44]. Metzger was the one that proposed that 2-hours postprandial glycemia should be used in GDM with the limit of 120 mg/dl [34]. Two clinical studies compared the blood glucose determination concluding that 1-hour glycemia is superior, but with two important biases—lack of randomization and low statistical power [45, 46].

A randomized clinical trial demonstrated that patients who adjusted insulin doses based on 1-hour postprandial glycemia had a lower risk of giving birth to a macrosomia, or to have a cesarean procedure; also, the risk for neonatal hypoglycemia was smaller [47]. Not only the glycemic values *per se* is important, but also the pregnant women with GDM should be taught to estimate their carbohydrate intake and physical activity and adjust the insulin doses. Other factors that cannot be influenced are a hormonal secretion from the placenta, daily cortisol secretion variability that contributes to glucose excursions. Sivan et al. observed in their study a pattern in which 1-hour postprandial glycemia is abnormally raised in the morning, and 2 hours postprandial glycemia is abnormally raised in the evening [48].

The frequency of determination is as much as necessary. Based on a randomized control trial (RCT) the initial recommendation for SMBG is 4 tests per day, with the possibility to lessen the number of determinations according to if the patient has good control and the fetal morphology is normal [49]. In basal-bolus insulin-treated GDM 7 tests per day are recommended, but patient adherence is weak (a mean of 4.2 in an observational study) [50].

The limit for SMBG consists in the accuracy bias: lowering hematocrit by dilution makes the capillary glucose to be overestimated. Some glucometers have included in their software functions to correct the hematocrit values, but the majority uses colorimetric and amperometric methods that depend on it. Considering the tight glycemic control required during pregnancy and the fact that insulin doses are

adjusted based on SMBG, some researchers recommend that the bias and imprecision should be set at below 2% and the meters be verified according to international quality criteria [51].

3.5.3 Continuous interstitial glucose monitoring (glucose sensors, CGMS)

Systems for interstitial glucose monitoring have been used together with insulin pumps in type 1 diabetes pregnancies in RCTs and observational studies [52, 53]. In GDM pregnancies data come from small observational studies where they showed benefit for disclosing high and low glycemic excursions missed by SMBG [54].

Glycemic sensors can be used as a guide for therapy initiation, as demonstrated by Kestilä et al. [55]. The anti-diabetes medication was introduced in a higher proportion of GDM women with CGMS versus SMBG. Nevertheless, there were not any significant differences for the perinatal endpoints. The long-term impact of glycemic control during pregnancy is not known; therefore, the benefit of this intervention must be balanced with unnecessary treatment. The techniques for monitoring blood glucose are summarized in **Table 4**.

All these efforts in using the best method for monitoring insulin therapy in GDM are to maintain glycemic control for preventing fetal and maternal complications.

3.6 Fetal complications associated with insulin therapy

3.6.1 Neonatal hypoglycemia

Glucose is a nutrient that freely crosses the placenta from maternal to fetal circulation, to assure the energy required for growth. Immediately after birth, the glucose source disappears with a physiologic “hypoglycemia” in the blood of the newborn that triggers the secretion of counterregulatory hormones (glucagon, steroids, catecholamines, growth hormone). In GDM pregnancies, the glycemia is continuously raised and determines a consecutive higher secretion of insulin that makes hypoglycemia more severe and prolonged than in normal newborns [56–59].

Regimen	SBGMS	CGMS
GDM with diet or oral antidiabetics	Fasting 1 hour postprandial	- Fine-tune insulin dosing - Nocturnal hypoglycemia
GDM with basal insulin	Fasting 1 hour postprandial Bedtime	- Nocturnal hyperglycemia - Postprandial hyperglycemia
GDM with premixed insulin	Fasting 1 hour postprandial Dinner preprandial 1 hour postprandial	
GDM with basal bolus	Fasting Preprandial (lunch, dinner) 1 hour postprandial	

Table 4.
Insulin glucose monitoring techniques [adapted from American Association of Clinical Endocrinologist and American College of Endocrinology].

Neonatal transient hypoglycemia could have implications in the neurocognitive development as was shown by magnetic resonance imaging [60]. Also, it has psychological implications on the mother-child relationship because they are separated after birth for treatment. Hence, based on their study results, Voormolen et al. recommend screening all newborns from GDM women in the first 12 hours after birth because the majority of the events occur in this interval, with a higher incidence being in the insulin-treated group [58].

A series of studies demonstrated that newborns of GDM patients that were treated with metformin had fewer hypoglycemic events than those of women treated with insulin [21, 61]. Insulin analogs have a lower rise in postprandial glycemic values without elevating hypoglycemic risk and should be preferred to human insulins [29, 33].

Regarding sulfonylureas, a meta-analysis demonstrated that glyburide treatment GDM had a higher risk of neonatal hypoglycemia and also macrosomia than the metformin-treated GDM [62].

3.6.2 Congenital anomalies

The relationship between insulin therapy and congenital anomalies was studied, especially in type 1 diabetes. The most important confounding factor is glycemic control. Although some case reports indicate an association between the use of insulin lispro and the risk of teratogenesis [63], another meta-analysis supports the fact that it is safe for use [64]. This risk could be explained by mitogenesis stimulation by binding with a higher affinity for IGF-1 receptors. Lispro insulin has a 1.5 and insulin glargine a 6.5 fold increase of receptor binding [65]. There are only retrospective studies that indicate glargine as safe insulin in pregnancy [66].

3.7 Birth complications associated with insulin therapy

3.7.1 Cesarean section (CS)

A Cochrane analysis of 1481 women with GDM showed that in the treatment group there was a higher number of induced labors versus the group with standard antenatal care, but with no difference regarding the number of births by CS [35]. Another meta-analysis did not demonstrate a correlation between the use of different types of insulin-like aspart, lispro and the birth by CS [67, 68]. Although the risk is not influenced by insulin treatment, it can be reduced by induction of labor (IOL) in 38th–39th week of gestation with better outcomes for the fetus [69].

3.7.2 Vacuum-assisted birth

Although pre-gestational diabetes raises the risk for vacuum assisted birth (shoulder dystocia, humerus, clavicle, skull fracture, Erb's palsy, subarachnoid or subdural hemorrhages, asphyxia, convulsion), in GDM the risk was similar to that in the general population and could not be related to insulin therapy [68, 70]. A particular situation is with GDM that appeared in pregnancies obtained by assisted reproductive technology where the risk for perinatal and obstetrical complications is probably increased by the adverse effect of hyperglycemia, not by insulin treatment [71].

3.7.3 Fetal morbidity

Evidence that indicates a higher risk for fetal morbidity and mortality in GDM is scarce and less pronounced as in pre-gestational diabetes. Current decisions of IOL

as compared to expectant management should be individualized because the studies lack in this area. An RCT that showed that there is no difference between the two strategies regarding morbidity, but the IOL reduces the risk for shoulder dystocia in the macrosomic fetus [72]. The use of insulin analogs like detemir does not influence the morbidity [73].

3.8 Maternal complications associated with insulin therapy

3.8.1 Maternal hypoglycemia

Hypoglycemia threshold is specific for every individual. In pregnancy, there is a reduction of this threshold by 20% [74]. Patients with GDM that are treated with insulin must maintain a glycemia above 3.7 mmol/l (66 mg/dl) according to CDA, or above 3.9 mmol/l (70 mg/dl) according to ADA [7].

Insulin analogs are superior to human insulin because the hypoglycemic events are less frequent in type 1 diabetic pregnancies [75]. The use of multiple daily injections is as effective as continuous subcutaneous insulin infusion [76].

Maternal hypoglycemia affects the fetus just in severe cases when is associated with loss of consciousness or secondary to trauma. Also, it was observed that repeated episodes could lead to growth over the 90th percentile [77]. These episodes are more likely to be present in the first trimester in women who had pregestational diabetes than in GDM [74].

3.8.2 Hypertension

There is moderate quality evidence that indicates higher hypertension associated hypertension without giving details in insulin-treated GDM. This fact should be further researched because it is in contradiction with a non-modified risk for pre-eclampsia [68].

3.9 Intrapartum management

During the latent phase of labor hepatic gluconeogenesis is sufficient for providing the caloric requirements, but becomes exiguous during the active phase when intravenous glucose is perfused.

The study of Rosenberg and collab. demonstrated there is no significant difference in neonatal hypoglycemia, neonatal injury, Apgar score at 1–5 minutes in patients with insulin therapy that were managed with two approaches: dextrose 5% 125 ml/h with a simultaneous insulin drip (adjustable rate 0.5–2.5 u/h) or dextrose 5% alternating with ringer lactate (125 ml/h) and insulin introduction when the targets are exceeded [77]. Other researchers recommend dextrose 10% with an insulin drip [78].

Lowering maternal glycemia is necessary for preventing neonatal hypoglycemia, balancing this risk with that for ketosis. Capillary blood glucose should be tested every hour and urinary ketone bodies every time is possible [77]. ACOG agreed to the protocol proposed by Coustan [79] for maintaining a mean intrapartum glyce-mic value of 100 mg/dl. For this, blood glucose should be tested every 2 hours with adjustments in insulin perfusion rates.

Women with GDM or type 2 diabetes, which were treated with oral therapy have a low insulin requirement and in most cases do not need treatment during labor. Thus, CDA recommends a “watchful waiting” and insulin initiation just in cases where glycemia is above 146 mg/dl (7.0 mmol/l) [19]. Ryan mentions the same principle in a review published before—if GDM pregnant had a necessary below 0.5 u/kg/day, they

could be initially monitored. Otherwise, patients with type 1 diabetes or type 2, GDM with a necessary above this limit will need insulin perfusions [78]. Insulin perfusion rates could be adjusted using sliding scales as proposed by Dude [80].

Although most of the studies use protocols for intravenous insulin administration, patients with insulin pumps can choose to keep their device during labor [81, 82]. This is recommended in centers with experience because during labor they can become unable to handle the pump given the pain, or some incidents like catheter avulsion could appear. In these cases, the patient is informed that a switch to an insulin drip is needed [19].

Another problem comes out when betamethasone is administered for premature birth. In patients with type 1 diabetes, an increase up to 40% of all doses during the next 5 days assures an adequate glycemic control [83]. A retrospective analysis of insulin drips in pregnant with GDM injected by a standard anticipatory protocol and with higher doses was associated with improving glycemic variability and decreasing by 25% the absolute risk for neonatal hypoglycemia [84].

3.10 Postpartum management

Insulin requirements drop quickly after giving birth and women are exposed to hypoglycemia. Patients with GDM usually do not need insulin, and women with type 1 and type 2 diabetes return to the previous regimen, but at doses that are at 60% of the antepartum necessary [85]. In the case where the doses are not remembered, half of the third-trimester dose could be injected. Another alternative is calculating dose per kilogram. With an insulin pump, the doctor will titrate downward the basal rate and boluses on a similar algorithm or adjust based on the information from glucose sensors for newer models.

Breastfeeding influences insulin sensibility: as the frequency of lactation increases, the HOMA and ISI (0, 120) have better values [86], so during breastfeeding the insulin requirement falls by 10% [87].

3.11 Future research directions

There is a lot of missing evidence in optimal treatment for GDM. Insulin treatment could be improved by developing automatic algorithms for calculating the appropriate doses like that proposed by Dinglas [88]. Moreover, fetal morbidity can be influenced by better monitoring like using glucose sensors that are more accurate in the hypoglycemic range [89–91].

Micro-RNAs are now extensively studied in different domains and might apply to diagnosing and selecting GDM patients that require insulin treatment [92].

Not eventually, the whole perspective of insulin therapy will change if the oral bioavailability of this peptide hormone will be enhanced. Polymeric nanocarriers and mucoadhesive discs were studied in diabetic rats and are the future expectation for mothers with diabetes [93].

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Conflict of interest

None.

Notes/thanks/other declarations

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