THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (March–April 2014) 64(2):82–90
DOI 10.1007/s13224-014-0525-4

REVIEW ARTICLE

Gestational Diabetes Mellitus: Insulinic Management

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Received: 22 February 2014 / Accepted: 24 February 2014 / Published online: 18 March 2014

Abstract Diabetic pregnancies have attendant risks. Adverse fetal, neonatal, and maternal outcomes in a diabetic pregnancy can be avoided by optimum glycemic control. Most pregnancies with GDM can be managed with non-insulinic management, which includes medical nutrition therapy. However, many necessitate concomitant insulinic management. The new insulin analogs present undoubted advantages in reducing the risk of hypoglycemia, mainly during the night, and in promoting a more physiologic glycemic profile in pregnant women with diabetes. Rapid-acting insulin analogs seem to be safe and efficient in reducing postprandial glucose levels more proficiently than regular human insulin, with less hypoglycemia. The long-acting insulin analogs do not have a pronounced peak effect as NPH insulin, and cause less hypoglycemia, mainly during the night. The review focuses on glycemic goals in pregnancy, insulinic management of GDM, and posology of insulin and its analogs. Clear understanding of the insulinic management of GDM is essential for women's health care providers to provide comprehensive care to women whose pregnancies are complicated with diabetes and rechristen the ''*diabetic capital of the world*'' to the ''*diabetic care capital of the world*.''

Keywords GDM · Insulin · Pregnancy · Aspart · Lispro · Detemir · Diabetes

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Introduction

A recent publication on the first global estimates for hyperglycemia in pregnancy (HIP) [1] has brought out that 16.9 % of total pregnancies globally were affected by some form of hyperglycemia in 2013, which translates to 21.4 million live births at risk of being exposed to a hyperglycemic intrauterine milieu, and gestational diabetes mellitus (GDM) being responsible for an estimated 84 % out of these. South East Asia (SEA) region had the maximum prevalence at 25 %, and India is standing tall at 27.5 % against a global average of 16.9 %. Country-specific estimates have further brought out that India had the highest number of women affected by HIP with an estimated 5.7 million cases in 2013, followed by China with 1.2 million. Comparatively, USA had just 350,000. The problem magnitude is huge and is all set to increase in years to come.

Pregnancy complicated with diabetes constitutes a significant challenge for health care professionals worldwide. Pedersen hypothesis drives the contemporary management of GDM, which holds that endogenous fetal hyperinsulinemia,

which is a response to fetal hyperglycemia, is responsible for fetal macrosomia and other metabolic sequelae in an infant of diabetic mother [2]. Fetal hyperglycemia is a direct reflection of maternal hyperglycemia, because glucose readily traverses the placenta whereas insulin does not. Therefore, diabetic fetopathy can be largely prevented by preventing maternal hyperglycemia. The cornerstone of management of a diabetic pregnancy is an attempt to keep maternal glucose as close to normal as possible.

Glycemic Goals in Pregnancy

A recent review emphasized the importance of having normative data for maternal glycemia when formulating therapeutic goals [3]. Supported by the available literature at that time, which was indeed not very far back, the consensus on the recommendations of the Fourth International Workshop-Conference on GDM was brought out, recommending the treatment goals to maintain fasting maternal capillary glucose at <96 mg/dl (<5.3 mmol/l), and <120 mg/dl (<6.7 mmol/l) 2 h after starting the meal. They remain unchanged in the fifth workshop too. However, the authors did emphasize that these recommendations were not based on glycemic values higher than those normally recorded in pregnancy, and they simply referred to glycemic levels associated with pregnancy outcomes.

A sizeable number of women with GDM whose glucose values are inside the current targeted therapeutic ranges also deliver macrosomic babies. It is accepted that glucose plays a key role in fetal growth; still, this paradox accentuates the likely role of other nutrients in fetal growth. It also stimulates to re-examine the definition of "normal" maternal glycemic patterns and its effects on fetal growth. Treatment targets may probably require revaluation.

The optimal therapeutic targets remain untested in randomized trials; therefore, evidence is extremely limited to guide these targets. A recent review [4] of 12 studies spread over half a century including a total of 255 pregnant women with normal weight and glucose tolerance reported the weighted average glucose values (±1 SD) as 71 ± 8 mg/dl fasting, 109 ± 13 mg/dl at 1-h postprandial, and 99 ± 10 mg/dl at 2-h postprandial. This seems to be the best assessment of normoglycemia during pregnancy till date. However, it brings forth that the current therapeutic targets for a diabetic pregnancy are all 20–30 mg/dl higher than average values in a normal (read, non-diabetic) pregnancy, which may well explain the macrosomia among infants of diabetic mothers, even when they have glycemic control within the presently designated therapeutic targets. Hernandez et al., based upon their calculated average glucose values in pregnant non-diabetic women, proposed targets of 81 mg/dl for fasting, 122 mg/dl for 1-h postprandial, and 110 mg/dl for 2-h postprandial. This, seen in backdrop of Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study [5], which found that there is a continuous linear relationship between increasing maternal glucose and large for gestational age (LGA), stands ground. Also, treatment trials such as the Australian Carbohydrate Intolerance Study (ACHOIS) [6] and Maternal–Fetal Medicine Units (MFMU) Network trial [7] corroborated that the risk of LGA and other adverse outcomes can be reduced with diet and medication designed to lower glucose, even when it is only mildly elevated.

Glycemic control during pregnancy is a balancing act in that hyperglycemia leads to LGA babies, but a very strict control may initiate frequent maternal hypoglycemic episodes and small-for-gestational age (SGA) babies. These challenging factors bequeath a state of equipoise. Presently available evidence suggests that a mean plasma glucose around ~105 mg/dl helps avoid either of these adverse pregnancy outcomes [8]. More research may bring in more evidence-based therapeutic targets. But, presently, treatment must aim at achieving target of fasting plasma glucose ~90 mg/dl and a 2-h postprandial ~120 mg/dl, which is also the therapeutic target of the current Indian guidelines on diagnosis and management of GDM [9], which helps attain a mean plasma glucose ~105–110 mg/dl and to obtain birth weight appropriate for gestational age (Table 1). Additionally, women with pre-existing T1DM or T2DM should strive to achieve glycated hemoglobin (HbA1c) value of ≤6 %.

Diabetic Pregnancy: Insulinic Management

A diagnosis of GDM mandates treatment to lower the risk of perinatal complications. Although majority of women with GDM are able to meet therapeutic targets with medical nutrition therapy (MNT), still many of them would require pharmacotherapy. Over the years, insulin has been the treatment of choice for any type of diabetes during pregnancy and preferred over oral anti-diabetic agents due to its better safety and efficacy to achieve good glycemic control.

Although a recent ACOG practice bulletin on GDM [10] has issued a level ''A'' recommendation that when pharmacologic treatment of GDM is indicated, insulin and oral medications are equivalent in efficacy, and either can be appropriate first-line therapy, still, till date, insulin remains

Table 1 Target blood glucose levels [9]

Fasting PG (mg%)	2-h PPG (mg%)	Mean PG (mg%)
80–90	110–120	100–110

the only FDA-approved anti-diabetic drug in pregnancy, and in many women with GDM, it remains the gold standard for treatment when they fail to achieve euglycemia on MNT alone. However, intensive antenatal insulin treatment (AIT) also remains the most resource-intensive management component in GDM. It would have been a win–win situation for all if there can be an improved risk stratification allowing triage. Recently, an Australian study [11] tried to identify patients of GDM who shall need insulin therapy by a risk-prediction tool based on maternal clinical and biochemical characteristics at diagnosis. It identified many significant independent risk factors for AIT, particularly measures of glycemia, time of diagnosis, and family history of diabetes. Amazing was the lack of predictive power encompassed by these risk factors, with only 9 % of the risk for AIT being attributable. In 3,009 GDM patients it studied, almost 50 % of the cohort finally required AIT, which is a relatively high proportion. However, only 1.3 % had a predicted probability of insulin usage of 90.1–100 %, and indeed many with a low calculated risk had a relatively high rate of insulin use. It concluded that lower blood glucose range at diagnosis does not necessarily transform in lower ranges during rest of pregnancy and, conversely, some with high glucose levels at diagnosis can modify their glycemic levels to totally avoid insulin. This lack of glycemic stability throughout pregnancy may explain some of the risk in the lower glucose ranges seen in the HAPO study. Therefore, all patients with diabetes in pregnancy require an individualized care.

With the increasing incidence of GDM, quite a good number of them would require pharmacotherapy and a proportion of them would be treated with insulin. Since the number of women requiring AIT is set to increase in times to come, it is imperative that women's healthcare providers must be conversant with the latest developments in the insulinic management of GDM. The current review shall focus on the role of insulin, especially the newer insulin analogs, in management of GDM.

The Pre-Insulin Era

Medical literature reports less than 100 pregnancies in diabetic women before the advent of insulin in 1921, that too associated with >90 % infant mortality rate and a 30 % maternal mortality rate. Even till 1980, diabetic women were counselled to avoid pregnancy. [12] This thinking was justified because of the poor obstetric history in 30–50 % of them. It was only in mid and late 1980s that infant mortality rates finally improved, when treatment strategies emphasized better control of maternal plasma glucose levels. As the pathophysiology of a diabetic pregnancy got clarified and management programs achieved and maintained near normoglycemia throughout pregnancy, perinatal mortality rates have decreased to levels seen in the general population.

Advances in insulin therapy have enhanced the management of diabetes in pregnancy. In pregnancy, the goal is to achieve normal plasma glucose through the day without any hypoglycemia. The most effectual approach to accomplish optimal glycemic control is to mimic physiologic insulin levels through frequent administration. This necessitates intensive insulin treatment.

The Insulinic Era

AIT is designed to mimic the physiologic insulin secretion by pancreas. Women with GDM produce insulin endogenously, but cannot support the increased insulin requirement to counter the diabetogenic placental hormones to maintain euglycemia. Insulin replacement is typically divided into basal and prandial insulin. Basal insulin contains hepatic glucose production in fasting state and in-between meals, and prandial insulin moderates meal concomitant glucose excursions.

Historically, regular human insulin (RHI) and neutral protamines Hagedorn (NPH) are the types of standard insulins which have been used for treatment of diabetes in pregnancy. Regular insulin is prepared by adding zinc atoms to dimers. On subcutaneous injection of RHI, it self-associates to form hexamers, which further need to disassociate into the monomeric form for its absorption through the capillary wall. The time required for disassociation is responsible for delayed absorption leading to a slower onset of action compared to endogenous insulin, resulting in increased risk of post-meal hyperglycemia. The same slow diffusion into circulation leads to delayed peak action as well as a longer duration of action compared to endogenous insulin. Therefore, at times, the preprandial administration of RHI is unable to control the peak postprandial plasma glucose and at the same time delayed peak action and a longer duration of action may result in inappropriate hyperinsulinemia before the next meal resulting in preprandial hypoglycemia. Thus, RHI is unable to mimic the physiologic insulin kinetics resulting in an unacceptable glycemic profile at times.

There are also some limitations with respect to intermediate human insulin. NPH has duration of action about 16–18 h and is unable to provide once-daily basal insulin. Night-time administration of NPH results in an unphysiologic rise in insulin concentration in the early-morning hours and risk of hypoglycemia. Moreover, prior to injection, the intermediate human insulin needs to be re-suspended adequately otherwise it may lead to inaccurate dosing and risk of hyper- and hypoglycemia [13].

Though widely used, insulin profiles of RHI & NPH do not mimic the in vivo state. Unfavorable pharmacokinetics

of RHI and NPH make aggressive glycemic control difficult. This increases the risk of major hypoglycemia and other potential adverse materno-fetal outcomes. Insulin analogs were developed to overcome the pharmacokinetic limitations of RHI and NPH.

The Era of Insulin Analogs

An insulin analog is a modified form of insulin, differing from natural insulin but still retaining its function in the human body. Biological engineering of the insulin molecule, with the substitution of 1 or 2 amino acids or minor chemical alteration, has improved pharmacokinetic profiles. This has resulted in two types of insulin analogs: rapidly acting and long acting. Rapidly acting insulin analogs (RAIA) are more readily absorbed from the site of injection and, therefore, act faster than RHI. They are designed to supply the bolus level of insulin needed after a meal. The long-acting insulin analogs are released slowly over a period of between 8 and 24 h, designed to supply the basal level of insulin for the day [14].

RAIAs, lispro and aspart, better imitate physiologic postprandial insulin secretion, and consequently, the glucose levels return to normal sooner than they do with the traditional RHI. Both lispro and aspart have been found to be safe and efficacious for pre-meal use in pregnancy [15]. Maternal glucose freely crosses the placenta, but maternal insulin does not do so unless bound to IgG antibody, which carts it through the placenta; or insulin is forced across the placenta by high perfusion. Fetal hyperinsulinemia is supposed to be instrumental in diabetic fetopathy. Thus, exogenous insulins that cross the human placenta should preferably not be used in management of diabetes complicating pregnancy. It is a known fact that maintenance of postprandial glycemic control decreases the peril of glucose-mediated fetal macrosomia. RAIAs do better postprandial glucose control vis-à-vis concentrations resulting from care with human regular insulin, and also do not transfer through the human placenta, and, therefore, should be cogitated as suitable therapeutic candidates during pregnancy for management of diabetes. Pharmacological characteristics of insulins are illustrated in Table 2.

As of now, basal insulin therapy for GDM may continue to focus on the use of NPH insulin, along with evolution of detemir which has recently been approved for usage in pregnancy. Contrariwise, RAIAs are now the preferred choice for prandial insulin dosing, because of their superior pharmacokinetics, commanding greater patient satisfaction, and improved quality of care. Although majority of clinical experience and date with insulin analogs in pregnancy has gathered in women with pre-existing diabetes, the doctrines of same clinic therapeutics with these newer insulin formulations can be extrapolated to women with GDM.

Rapid-Acting Insulin Analogs

Insulin Aspart

Insulin aspart is produced by substituting the proline at position 28 on the β-chain of the insulin molecule with negatively charged aspartic acid. This substitution is responsible for fast dissociation of hexamers into monomers in subcutaneous tissue resulting in very rapid onset of action. Following subcutaneous injection of insulin aspart, the peak action is reached by 31–70 min and acts for out 2–4 h. A randomized controlled trial in 322 pregnant women with Type 1 diabetes has not shown any difference in safety of aspart compared with RHI [16]. It is now approved for use in pregnancy offering a valuable treatment option. The clinical trials on efficacy and safety of insulin aspart in pregnancy are summarized in Table 3.

Insulin Lispro

Insulin lispro is the another RAIA produced by inverting lysine at position 28 and proline at position 29 on the β-chain of the insulin molecule. These inversions lead to conformational changes that result in a quick dissociation of hexamers into monomers in subcutaneous tissue; as a consequence, insulin lispro has a very rapid action. On subcutaneous injection, peak action is reached at 1 h and the duration of action is 2–4 h [25]. Insulin lispro has also been approved by US FDA for use during pregnancy.

Several clinical studies show that lispro in comparison to RHI has lower hypoglycemic episodes before breakfast, lower postprandial hyperglycemia, and higher reduction in HbA1c levels in pregnancy. However, no differences in rate of cesarean sections, frequencies of preterm delivery, preeclampsia, or other neonatal morbidities between the treatment with lispro and RHI were observed. The results of clinical studies on efficacy of insulin lispro in pregnancy have been summarized in Table 4. This data suggest that insulin lispro may be considered a treatment option in pregnant with GDM.

Insulin Glulisine

Insulin glulisine is the latest rapid-acting insulin analog approved by US FDA for clinical use in 2004, but not yet approved for pregnancy usage. Its pharmacologic action profile is similar to both insulin lispro and insulin aspart. Insulin glulisine has been studied for use in both types 1 and 2 diabetes; however, clinical data are presently not available on the use of insulin glulisine in pregnancy.

Table 2 Pharmacologic characteristics of standard insulin and insulin analogs

Insulin	Onset of action (min)	Time to peak concentration (min)	Duration of action (h)
Short/rapid acting			
Regular insulin	30–60	90–180	8–12
Insulin lispro	10–15	30–90	3–4
Insulin aspart	10–15	30–70	2–4
Insulin glulisine	10–15	30-90	3–5
Long acting			
NPH	60–120	240–480	12–18
Insulin glargine	60–120	None	Up to 24
Insulin detemir	60–120	None	Up to 24

Table 3 Efficacy and safety of insulin aspart in pregnancy

Author	Type of study	*n*	Type of diabetes	Type of insulin	Results
Zhou and Fan [17]	CT	80	GDM	Aspart versus regular	Comparable efficacy and safety. No significant inter-group difference in outcomes of pregnant women & their babies
Heller et al. [18]	RCT	99	T1DM	Aspart versus regular	Initiation of insulin aspart preconception rather than during early pregnancy may result in a lower risk of severe hypoglycemia
Lloyd et al. [19]	RCT	322	T1DM	Aspart versus NPH	More live births at term, without increasing total costs
Hod et al. [20]	RCT	322	T1DM	Aspart versus regular	Fetal outcome comparable with a tendency toward fewer fetal losses and preterm deliveries
Mathiesen et al. [16]	RCT	322	T2DM	Aspart versus NPH	Reduced major hypoglycemia and lower postprandial glycemia
Pettitt et al. [21]	RCT	27	GDM	Aspart versus regular	More effective in decreasing postprandial glucose levels, Overall safety and effectiveness comparable.
Di Cianni et al. [22]	RCT	96	GDM	Aspart versus lispro versus regular	Both RAIAs associated with better postprandial maternal glucose control and anthropometric measures in newborns
Pettitt et al. [23]	RCT	15	GDM	Aspart versus regular versus no insulin	Better lowering postprandial excursions in aspart group
Lindholm et al. [24]	Case–control	886	T1DM and T2DM	Aspart versus regular	Antibodies specific to insulin aspart were rare; their levels remained undetectable in most patients throughout the studies, with mean levels below the upper normal limit

Table 4 Efficacy and safety of insulin lispro in pregnancy

Author	Type of study	*n*	Type of diabetes	Type of insulin	Results
Colatrella et al. [26]	Retrospective	89	T1DM and GDM	Lispro protamine versus NPH	Pregnancy outcome was similar, except for a lower insulin requirement.
Durnwald et al. [25]	Prospective	107	T1DM and T2DM	Lispro versus regular	Improved glycemic control and lower total insulin requirements. Perinatal outcomes similar between women treated with both types of insulin.
Cypryk et al. [27]	Retrospective	71	T1DM	Lispro versus regular	Comparable course of pregnancy and the perinatal outcome
Persson et al. [28]	RCT	33	T1DM	Lispro versus regular	Reduced postprandial glycemia after breakfast and slightly higher rate of hypoglycemia
Batthacharyya et al. [29]	Retrospective	157	GDM	Lispro versus regular	Significant decrease in HbA1c levels and greater satisfaction
Jovanovic et al. [30]	RCT	42	GDM	Lispro versus regular	Less hypoglycemic episodes before breakfast; less postprandial hyperglycemia; more reduction in HbA1c levels at the 3rd trimester

Table 5 Efficacy and safety of insulin detemir in pregnancy

Author	Type of study	*n*	Type of diabetes	Type of insulin	Results
Callesen et al. [35]	Retrospective	113	T1DM	Insulin detemir versus glargine	Hemoglobin A1c levels and the incidence of severe hypoglycemia were comparable at 8 weeks. Proportion of pre-eclampsia, preterm delivery, and infants LGA was also comparable in both groups.
Hod et al. [34]	RCT	274	T1DM	Insulin detemir versus NPH	Well tolerated, comparable perinatal outcomes and no safety issues.
Lambert and Holt [13]	Case report	1	T1DM	Insulin detemir	Bedtime detemir may indeed favor improved glycemic control during pregnancy, reducing the risk of hypoglycemia.
Mathiesen et al. [36]	RCT	310	T1DM	Insulin detemir versus NPH insulin	Non-inferior; fasting plasma glucose (FPG) was significantly lower; Major and minor hypoglycemia rates during pregnancy were similar between groups.
Shenoy et al. [37]	Retrospective	18	T1DM and T2DM	Insulin detemir	Maternal outcomes were satisfactory, with only one woman having severe hypoglycemia, and no progression of retinopathy or nephropathy.
Lapolla et al. [32]	Retrospective	10	T1DM	Insulin detemir	Glycemic control improved, and HbA1c progressively decreased. None of the women developed or underwent progression of diabetic retinopathy, and none had diabetic nephropathy or neuropathy.

Long-Acting Insulin Analogs

Insulin Glargine

Insulin glargine is the first long-acting insulin analog approved by US FDA for clinical use in 2000 for clinical use in diabetes, with onset of action approximately after 90 min of injection and lasting for about 24 h. Although the clinical efficacy and safety of Insulin glargine have not been studied in randomized controlled trials in pregnancy so far, there are several case reports and one case–control study on its use during pregnancy. Price et al. [31] in a case–control study compared Glargine versus NPH in T1DM and GDM women and found no association with increased fetal macrosomia or neonatal morbidity with use of glargine in pregnancy. Currently, the use of insulin glargine in pregnancy is not approved and well-planned controlled trials are needed to determine the safe use in pregnancy.

Insulin Detemir

Insulin detemir is a long-acting recombinant human insulin analog produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae*. The chemical modification, with covalent acylation of the amino group of lysine in B29 position, imparts a neutral pH to the insulin molecule. On subcutaneous injection, it is slowly absorbed and binds to albumin through a fatty-acid chain attached to the lysine at residue B29 resulting in reduction in its free level and a slow distribution to peripheral target tissues with a duration of action of up to 24 h. By the virtue of these properties, it has a consistent pharmacokinetic/pharmacodynamic profile, with lower intra-subject variability in terms of glucose-lowering effect compared with either NPH or insulin glargine. Insulin detemir has been approved for clinical use since 2006 by US FDA, and in 2012 has been approved for use in pregnancy, being presently the only basal insulin analog to achieve FDA pregnancy category B classification. This approval provides clinicians with a long-acting insulin analog option in management of pregnancy diabetes.

Clinical trial data have demonstrated that insulin detemir provides similar glycemic control, but with lower rates of hypoglycemia and less weight gain, than NPH insulin in non-pregnant diabetic women [13]. Two case reports have documented the use of insulin detemir in 11 T1DM women in the preconceptual period and pregnancy [32, 33]. All women were maintained on this insulin due to significant risk of nocturnal hypoglycemia. No adverse maternal or neonatal effects were identified. Comparative study between insulin detemir and NPH insulin during pregnancy has demonstrated that fetal outcomes did not differ between treatments and there was a significant improvement in fasting plasma glucose with insulin detemir without an increased incidence of hypoglycemia, including nocturnal episodes [34]. Table 5 summarizes the data on effectiveness and safety of detemir in pregnancy.

Premixed Insulins

Although effective at improving postprandial glycemic control with a more physiologic profiling, RAIAs require administration before every meal, and addition of basal

insulin may be needed. This results in a complex basal-bolus regimen requiring at least 4 injections daily. There is an inverse relation between patient compliance with treatment and regimen complexity [38]. Therefore, it is imperative that treatment be simplified as much as feasible. Premixed insulin formulations are the key to simplifying insulin therapy by reducing injection frequency. Although premixed human insulin 30 (BHI 30) comprising of 30 % short-acting RHI and 70 % intermediate-acting NPH insulin has been available for a long time, the ability of BHI 30 to mimic the endogenous insulin profile is compromised by the pharmacokinetics of its components. Alternatives based on RAIAs are available. Premixed insulin analogs are an opportune way to cover both prandial and basal insulin requirements in one injection. The formulations include a RAIA for prandial coverage and its protaminated counterpart for basal coverage and are available in different ratios of 30/70, 25/75, and 50/50 of rapid-acting and long-acting components. The premixed insulin analog provides better postprandial coverage and less hypoglycemic tendencies between meals.

Biphasic insulin aspart (BIAsp 30) comprises rapid-acting aspart combined with long-acting protamine-crystallized insulin aspart in a 30:70 ratio. It mostly requires a twice-daily dosing and conveniently provides an insulinic profile, which mimics the physiologic insulin release.

A randomized, open-label study [39] was conducted in 323 GDM women. Participants were randomly assigned to either premixed insulin aspart 30 (biphasic insulin aspart [BIAsp 30]) or premixed human insulin 30 (biphasic human insulin [BHI 30]). It was concluded that BIAsp 30 was non-inferior to BHI 30, producing comparable fetal outcomes. Based on final doses which were lower for BIAsp 30 to maintain the target levels, it may offer greater treat-to-target potential for pregnant women than BHI 30.

Insulin: Posology

Placental anti-insulin hormones coupled with an increased maternal cortisol level in concert with weight gain and decreasing exercise in pregnancy result in rise in insulin requirements. Pre-conception, 24-h insulin requirement is ~0.8 units/kg weight. However, in first trimester, there is a transient drop in insulin requirement and it falls to ~0.7 units/kg maternal weight. In early pregnancy, the placental passage of glucose and placenta taking over the role of progesterone secretion from corpus luteum with a transient drop in progesterone levels jointly decrease the insulin requirement in later part of first trimester. Further, there is a propensity of low-fasting and high-postprandial blood glucose level digressions in this period. Blood glucose control is unstable and carries a risk of nocturnal hypoglycemia. To add to it all, nausea and vomiting of pregnancy can further predispose to hypoglycemia. Not decreasing the insulin dosing by ~10 % of preconception dose can precipitate maternal hypoglycemia. As pregnancy advances, placenta produces increasing amounts of anti-insulin hormones, leading to progressive increments in insulin need. By second trimester, daily insulin requirement is back to pre-conceptional levels ~0.8 units/kg, and in third trimester, is ~0.9–1.0 units/kg pregnant weight [40]. Near term, insulin requirements may decrease again, specifically through the night, because of transfer of maternal glucose to fetus. These metabolic physiognomies signify a greater demand for short-acting insulin, which covers the meal, and also optimal dosing of intermediate-acting insulin, to assure a constant basal rate. Morbidly obese woman may need ~1.5–2.0 units/kg to overcome the combined insulin resistance of pregnancy and obesity. Twin pregnancies complicated by GDM require an approximate doubling of insulin requirement throughout pregnancy.

Dosing schedules vary according to type of insulin used. NPH and RHI can be medicated in 3–4 injections per day. Two-thirds of the total daily dose is to be given in the morning in a ratio of 2:1 NPH to RHI. The 2:1 proportion of intermediate- to rapid-acting insulin is based on the pattern of insulin release in normal pregnant women in the third trimester. Remaining one-third is given in the evening in a ratio of 1:1 NPH to RHI. This means thereby that one-sixth of the total daily dose is given as RHI at dinnertime and one-sixth of total daily dose is given at bedtime as NPH. Sometimes, an additional dose of rapid-acting insulin may be required to maintain euglycemia post lunch. Postprandial breakfast and before-lunch glucose levels are used to assess the adequacy of morning RHI. Glucose levels before dinner assess the adequacy of morning NPH dosing, and 2-h post dinner (or bedtime) levels assess the adequacy of evening RHI. Evening NPH insulin adequacy is assessed using the fasting glucose levels the next morning.

Subsequent adjustments in the various components of the insulin regimen are made based upon the corresponding glucose levels as explained above. Titration of insulin dose is based upon frequent self-monitoring of blood glucose. Four to six glucose readings are needed daily to optimize therapy (fasting and 1- or 2-h postprandial with the possible addition of pre-lunch and pre-dinner) and ensure a smooth increase of insulin as insulin requirements increase as pregnancy progresses. Although hypoglycemia remote from meal is rare in GDM, in case it happens should be straightaway managed with a 10–20 g of a mixed protein–carbohydrate snack. The administration of pure simple sugar in this scenario may lead to rapid elevation of glucose followed by rapid decline, whereas the mixed protein-carbohydrate snack dampens the variation. If there are

multiple hypoglycemic episodes, insulin doses require downward adjustment.

If RAIAs are used in place of RHI along with NPH, the total dosage can be dispensed in four injections a day. NPH is dosed as 2/3 of the total daily dose. Of the 2/3 daily dose of NPH, 2/3 is given in the morning and 1/3 at bedtime. RAIAs constitute the remaining 1/3 of total daily dose and are divided in three parts depending upon carbohydrate intake and administered before each meal. The dinner dose may need to be decreased to accommodate the morning NPH peak. If RAIAs are used with detemir in place of NPH, it can be administered in four injections per day. Approximately 40–50 % of the total daily insulin requirement is administered at bedtime as detemir, and the remaining insulin is divided into three doses with each meal. Again, the specific dose will depend on carbohydrate intake but could theoretically be divided equally for each meal. If we use premixed insulin analogs, the whole day requirement can be taken care of in two injections.

Conclusion

There is a tsunami of GDM, and it is a vicious cycle. It is undeniably proven now that diabetes is more prevalent among adults who were exposed to maternal diabetes in their intrauterine life [41]. The role of maternal inheritance in diabetes has been reported, and it is also indicated that intrauterine exposure to a diabetic environment increases risk of diabetes and obesity beyond that attributable to genetic factors alone. Preventing fetal hyperinsulinemia can check this to some extent, which in turn can be prevented by checking maternal hyperglycemia. This requires a strict glycemic control in a pregnancy complicated by diabetes. Non-insulinic with or without insulinic management, as required from case-to-case basis, can accomplish the same. Therefore, it is imperative upon the women's health care providers to take the lead to provide standard of care to women with GDM and rechristen the ''*diabetic capital of the world*'' to the ''*diabetic care capital of the world*'' [42].

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