

Treatment Considerations for Gestational Diabetes Mellitus and Long-Term Postpartum Options

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1. Introduction

Gestational diabetes mellitus is commonly defined as hyperglycemia with onset or first recognition during pregnancy. However, this definition of gestational diabetes does not exclude pregnant women with undiagnosed pre-existing diabetes that now accounts around 1% of diabetes mellitus cases in pregnancy. Prompt identification of pre-existing diabetes, if compared with women with gestational diabetes mellitus, is essential, for the reason that women with pre-existing diabetes are at risk of giving birth to infants with serious malformations, and adverse pregnancy outcomes are increased in this cluster, too. These include serious injury at birth, increased probability of cesarean delivery, and increased incidence of newborn admission in intensive care unit.

The incidence of gestational diabetes is unfortunately increasing, it accounts for 90% of cases of diabetes mellitus in pregnancy, and it has strong association with adverse pregnancy outcomes. Risk factors connected to gestational diabetes mellitus include older age, family history and previous history of gestational diabetes mellitus, obesity, polycystic ovary syndrome and high blood pressure (American Diabetes Association, 2009; Hedderson and Ferrara, 2008). If untreated, it may lead to diverse complications, such as fetal hyperinsulinemia, increased weight at birth, higher rates of cesarian deliveries, shoulder dystocia, more neonatal hypoglycemia, and is associated with concomitant preeclampsia in pregnant women. Therefore, given that gestational diabetes may have long-term pathological consequences for both mother and the child, it is important that it is recognized and correctly managed.

Treatment of gestational diabetes is aimed to maintain euglycemia and it involves regular glucose monitoring, dietary modification, life style changes, exercise, and, when necessary, pharmacotherapy. Insulin therapy is the first choice of treatment, although glyburide and metformin may be indicated, too. In women receiving pharmacotherapy scheduled monitoring of fetal well-being with antenatal tests should be pursued.

2. Non-pharmacological treatment

Self-monitoring of blood glucose is considered to be essential during pregnancy. This is supported, for example by the fact, that self-monitoring of blood glucose in women with

mild gestational diabetes positively correlates with reduced rate of fetal overgrowth and gestational weight gain (Hawkins, 2010). Moreover, taking into account that excessive gestational weight gain correlates with postpartum weight retention, regular monitoring of blood glucose during pregnancy might certainly have long-term benefits (Siega-Riz et al., 2009). Common fasting, preprandial and postprandial glucose tests are all recommended in order to attain adequate glycemic targets and reduce overall rate of large-for-gestational-age infant births (Aschwald et al., 2009; Jovanovic, 2008; Riskin-Mashiah et al., 2009). The frequency and timing of home glucose monitoring for gaining and maintaining target glucose levels should be individualized. Generally, the monitoring of blood glucose level is performed in the fasting state, and 1–2 hours after meals, too. Taking into account the increased risk of nocturnal hypoglycemia that may be present during the course of pregnancy; in pregnant women receiving insulin night testing or even continuous glucose monitoring might be suggested (McLachlan et al., 2007).

It is recommended that women diagnosed with gestational diabetes should have expert dietitian counseling to ensure that medical nutrition therapy supports euglycemia, adequate nutritional intake and controlled weight gain. Dietary recommendations should be individualized for each patient. Moderate carbohydrate restriction and proper distribution of daily meals should be emphasized. Namely, six meals per day are recommendable, including three major meals and three smaller ones - snacks. As a result, it has been shown that restriction of carbohydrates to 35–40% will decrease maternal glucose levels and improve maternal and fetal outcomes (Major et al., 1998). For pregnant women with body mass index >30 kg/m², a 30–33% calorie restriction is expected to reduce hyperglycemia and plasma triglycerides (Moore, 2010). Moreover, fetal-based strategy to govern maternal glucose control may notably improve outcomes for the fetus given that increased fetal abdominal circumference on an ultrasound (conducted between 28–34 weeks) has been found to be connected to increased insulin in amniotic fluid, thus directly revealing poor maternal glycemic control. Assessing the fetal response to maternal gestational diabetes mellitus by ultrasound measurement of fetal abdominal circumference starting in the second and early third trimesters and repeated every 2–4 weeks can provide useful information (in combination with maternal self-monitoring of blood glucose levels) to guide management decisions (Metzger et al., 2007).

Individually adjusted physical activity should be promoted, especially in overweight or obese women who are often insulin resistant and at risk for preeclampsia. Thus, the amount of physical activity consisting of 20 minutes aerobic training three days weekly for six weeks, has been shown to result in lower fasting glucose levels, lower glucose responses to a glucose challenge, and a lower glycated hemoglobin - HbA_{1c} (Jovanovic-Peterson et al., 1989). Avery et al. (1997) have also observed improved glucose levels in women who exercised 30 minutes 3–4 times per week. The delay in requirement of insulin was reported in another study involving resistance training three times per week (Brankston et al., 2004). Exercises may not be advisable if obstetrical contraindications exist, or in cases in which physical activity actually worsens glycemic control.

3. Pharmacological treatment

Insulin is the first-line pharmacological intervention for gestational diabetes and it should be initiated in women diagnosed with gestational diabetes or impaired glucose tolerance who did not achieve glycemic control within two weeks by the sole application of individualized

nutrition plan. During pregnancy, the main objective of insulin therapy will be to attain glucose levels similar to those before pregnancy. If indicated, at the beginning small doses of insulin are to be administered, and then insulin doses should be gradually increased. This should be accompanied by the appropriate administration intervals until target glucose levels are attained. Taking into account that insulin resistance rises during the whole pregnancy period, the insulin regimens must be continuously monitored, reviewed and modified. This is particularly significant during the third trimester of pregnancy when the required dosage of insulin usually increases. Hypoglycemia prevention measurements should be clearly explained to all pregnant women on insulin therapy. Still, insulin therapy is considered to be effective and safe, and it is regarded as the gold standard of pharmacotherapy for gestational diabetes. It has been well determined that the use of insulin to achieve glycemic targets reduces fetal and maternal morbidities. In this way, daily glucose control and diet that were associated with insulin treatment and additional obstetric interventions have been confirmed to reduce the incidence of shoulder dystocia and macrosomia (Horvath et al., 2010).

A diversity of protocols can be used, but multiple injections are considered to be the most effective. The majority insulin protocols include intermediate-acting insulins, such as isophane, and short-acting insulins, such as regular recombinant, as well the insulin analogues aspart and lispro. Although isophane is the intermediate-acting insulin of the first choice for women with gestational diabetes, evidences also support the use of short-acting insulin analogues in women who require pharmacological treatment of gestational diabetes. Moreover, the use of insulin analogs in pregnancy presents the potential benefits of more closely mimicking biological pancreatic insulin secretion compared to regular insulin (Klieger et al., 2008).

Insulin lispro is insulin analog with fast absorption rate and a short duration of action that improves postprandial glucose levels and reduces hypoglycemic episodes when injected immediately prior to meals (Anderson et al., 1997). In the study conducted by Jovanovic et al., (1999) it was of interest to compare the immunologic response to insulin lispro with that to regular human insulin, thereby assuring its safety for use in women with gestational diabetes, and to verify that it is effective. Anti-insulin antibody levels were similar in the two groups. Insulin lispro was not detectable in the cord blood. During a meal test, areas under the curve for glucose, insulin, and C-peptide were significantly lower in the lispro group. Mean fasting and postprandial glucose concentrations and end point Hb_{A1c} were similar in the two groups but the lispro group demonstrated fewer hypoglycemic episodes. Accordingly, in women with gestational diabetes mellitus, the use of insulin lispro enabled the attainment of near-normal glucose levels at the one hour post-prandial time point and was associated with normal anthropometric characteristics; whereas use of regular insulin was not able to blunt the one hour peak post-prandial response to a near-normal extent and resulted in infants with a tendency toward the disproportionate growth (Mecacci et al., 2003). Bhattacharyya et al. (2001) reported no increase in adverse outcome using lispro insulin in diabetic pregnancies, in either gestational or pre-gestational diabetes. Likewise, there was no difference in respect to congenital anomalies of gestational diabetic groups, which used either insulin lispro or regular human insulin (Aydin et al., 2008).

In consideration to insulin aspart use, it has been demonstrated that effective postprandial glycemic control in women with gestational diabetes mellitus who required insulin was brought about by insulin aspart through higher insulin peak and lower demand on

endogenous insulin secretion (Pettitt et al., 2003). In particular, the peak insulin concentration was higher and the peak glucose and C-peptide concentrations were lower with both insulin preparations than with no exogenous insulin. Moreover, glucose areas under the curve above baseline were significantly lower with insulin aspart, but not with regular insulin, than with no insulin. In another randomized, parallel, open-label, controlled, multicenter and multinational study of type 1 diabetes pregnancy the fetal outcome using insulin aspart was comparable with human insulin, with a tendency toward fewer fetal losses and preterm deliveries (Hod et al., 2008). In another study, insulin aspart was more effective than regular human insulin in decreasing postprandial glucose concentrations (Pettitt et al., 2007). The authors of this investigation found out that duration of insulin aspart injection 5 min before a meal rather than 30 min prior to meals offered a more convenient therapy for subjects with gestational diabetes mellitus. Moreover, overall safety and effectiveness of insulin aspart were comparable to regular human insulin in pregnant women with gestational diabetes mellitus.

Glyburide and metformin are oral antidiabetics that may be considered as second line agents in cases of gestational diabetes with poor glycemic control with insulin, or in women who refuse insulin. This is supported by the fact that when compared with insulin, administration of oral hypoglycemic agents was not associated with risk of neonatal hypoglycemia, caesarean section, or large-for-gestational-age babies births (Dhulkotia et al., 2010). No significant differences were found in maternal fasting or postprandial glycemic control, too. It appears that glyburide may be preferred, as metformin use is more likely to need supplemental insulin for glycemic control and in addition metformin crosses the placenta with possible long-term effects. It has been estimated that fetal levels of metformin may reach approximately half of maternal levels (Vanky et al., 2005).

The sulfonylurea glyburide is safe and effective at controlling glucose levels in majority of pregnant women with gestational diabetes mellitus. The study of Langer et al. (2005) was aimed to investigate the association between glyburide dose, degree of severity in gestational diabetes mellitus, level of glycemic control, and pregnancy outcome in insulin- and glyburide-treated patients. It has been reported that glyburide and insulin were equally efficient for treatment of gestational diabetes mellitus in all levels of disease severity. In earlier investigation it was also demonstrated that there were no significant differences between the glyburide and insulin groups in the percentage of infants who were large for gestational age, who had macrosomia, who had lung complications, who had hypoglycemia, who were admitted to a neonatal intensive care unit; or who had fetal anomalies (Langer et al., 2000). Glyburide is regarded as a pharmacologically active substance that minimally crosses placenta, as supported by different *in vitro* and *in vivo* investigations that demonstrated very low transplacental transport of glyburide to the fetal circulation. This is due to high plasma protein binding, short half-life, as well as its active transport from the fetus to the mother (Bertini et al., 2005; Koren 2001; Kraemer et al., 2006). In the study aimed to identify placental transporters potentially involved in limiting the transplacental transfer of glyburide to the fetus it was demonstrated that glyburide is preferentially transported by the breast cancer resistance protein pump and multidrug resistance-associated protein 3, that are highly expressed in placental tissues and limit the passage of therapeutic or toxic xenobiotics to the fetus (Gedeon et al., 2006). Unfortunately, poor clinical response to glyburide has been reported in women with higher fasting and postprandial glucose values on their oral glucose tolerance test or in the group of diabetic

women on diet therapy. Other identified predictors of glyburide treatment failure were advanced maternal age, earlier diagnosis of gestational diabetes mellitus, higher gravidity or higher parity (Kahn et al., 2006). Otherwise, glyburide can be recommended for women in whom insulin cannot be used. In that way, it has been confirmed that this oral hypoglycemic can be used safely and effectively during the second and the third trimester of pregnancy without increasing maternal or fetal complications when compared with insulin (Langer et al., 2000). Glyburide has been shown to be safe in breastfeeding, too (Feig et al., 2005). However, it has to be emphasized that in some investigations a glyburide-related increased risk of preeclampsia, macrosomia, neonatal hypoglycemia, admission to a neonatal intensive care unit; as well a need for phototherapy have been reported (Jacobson et al., 2005; Ramos et al., 2007).

The second oral antidiabetic drug used in gestational diabetes mellitus, as a monotherapy or with supplemental insulin, is metformin, a biguanide. It lowers blood glucose levels by decreasing hepatic gluconeogenesis, increasing peripheral glucose disposal and reducing intestinal glucose absorption (Hundal & Inzucchi, 2003). In average, up to half the women using metformin may require supplemental insulin. It has been demonstrated that women requiring supplemental insulin had a higher body mass index and had higher baseline glucose levels (Rowan et al. 2008). If compared to insulin, metformin was not associated with increased perinatal complications except of higher incidence of perinatal mortality if administered during the third trimester (Hellmuth et al., 2000). Although it may appear that metformin is safe alternative to insulin therapy, it does cross the placenta (Vanky et al., 2005) and scientific data are still not conclusive enough to recommend the standard use of metformin during pregnancy beyond the first trimester. Data that are more recent suggested that in women with gestational diabetes mellitus, not controlled with diet and exercise, who were then randomized to the metformin or the insulin arm, metformin has been shown to be an effective alternative to insulin in the treatment of gestational diabetes mellitus (Moore et al., 2007). This was substantiated by findings showing that difference in the rate of cesarean delivery was not statistically significant between the two groups, neither the neonatal statistics involving birth weight, Apgar score at 5 minutes, respiratory distress syndrome, hyperbilirubinemia, neonatal hypoglycemia or neonatal intensive care unit admission. Likewise, in investigation of Rowan et al. (2008) women with gestational diabetes mellitus at 20 to 33 weeks of gestation were randomly assigned to open treatment with metformin (with supplemental insulin if required) or insulin. The primary outcome was a composite of neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, 5-minute Apgar score less than 7, or prematurity. The rate of the primary composite outcome was comparable between the group assigned to metformin and the insulin group, suggesting that in women with gestational diabetes mellitus, metformin (alone or with supplemental insulin) was not associated with increased perinatal complications as compared with insulin. The retrospective data of Terti et al. (2008) have been also indicative for the assumption that metformin was effective in controlling gestational diabetes and was not associated with a higher risk of maternal or neonatal complications compared with insulin. Namely, there were no differences between the metformin-treated group and the other two investigated groups (women treated with insulin and women with no pharmacological treatment) in terms of maternal outcomes (total weight gain during pregnancy or after the diagnosis of gestational diabetes mellitus, pre-pregnancy hypertension, pregnancy induced

hypertension, pre-eclampsia etc.). In this investigation, no differences between the metformin-treated group and the other two groups were observed in relation to mean birth weights, prevalence of macrosomia, or gestational weeks at delivery. Finally, there were no differences between the groups in relation to other neonatal outcomes (small for gestational age, Apgar scores, umbilical artery pH or base excess, etc.). This drug is contraindicated in the case of preeclampsia, intrauterine growth restriction or placental insufficiency. Moreover, given that metformin crosses placenta, it could increase insulin sensitivity in the fetus, thus probably affecting growth and fetal hepatic glucose production.

4. Postpartum considerations

After delivery, it is fundamental that women receive the appropriate postpartum counseling, testing, and follow-up. In a long-term view, most women with gestational diabetes do not require insulin therapy following delivery. Nevertheless, glucose levels should be regularly checked after discharge, since it has been confirmed that the progression of gestational diabetes mellitus to type 2 diabetes increased steeply within the first 5 years after delivery and appeared to plateau after 10 years (Kim et al., 2002). It has been determined that progressive beta-cell failure to compensate for the ongoing insulin resistance correlates with progression from gestational diabetes mellitus to type 2 diabetes. Insulin resistance that presents as a high serum insulin concentrations in association with blood glucose concentrations that are normal or high, results from defects in insulin responsiveness in muscle, fat and liver. Therefore, screening for diabetes at regular intervals should be of paramount importance. In addition, among women with a family history of type 2 diabetes, those with prior gestational diabetes mellitus were even more likely not only to have cardiovascular disease risk factors, including metabolic syndrome and type 2 diabetes, but also to have experienced cardiovascular disease events, which occurred at a younger age (Carr et al., 2006). Moreover, the development of metabolic syndrome in children with increasing age is known to be related to maternal gestational diabetes mellitus, maternal glycemia in the third trimester, maternal obesity, neonatal macrosomia, and childhood obesity (Vohr & Boney, 2008). Consequently, post partum evaluation and management of reversible cardiovascular risk factors such as smoking, obesity, hypertension, and hyperlipidemia should be undertaken (Cheung, 2009).

It is confirmed that a good predictor of early postpartum development of diabetes is elevated fasting plasma glucose during pregnancy and, in women having positive tests to specific autoantibodies [anti-glutamic acid decarboxylase (anti-GAD); anti-protein tyrosine phosphatase ICA 512 (anti-IA-2)], higher incidence of diabetes by six months postpartum has been shown, too. In addition, it should be pointed out that some women with gestational diabetes mellitus, especially lean ones under 30 years of age who required insulin during pregnancy, could progress to type 1 diabetes. Therefore, women diagnosed with gestational diabetes should be screened for diabetes 6 to 12 weeks postpartum and should have subsequent screening for the development of diabetes or prediabetes (American Diabetes Association, 2009). An oral glucose tolerance test at three-year intervals has been also shown to be a beneficial approach for screening.

All women with gestational diabetes should be encouraged on a healthy lifestyle and in order to prevent diabetes and cardiovascular complications education on lifestyle modification should start in pregnancy and continue postpartum. In that way, usual

recommendations to promote postpartum weight adjustments and decrease the incidence of type 2 diabetes include breastfeeding, exercising at a moderate intensity, and modifications of nutrition for specific weight-loss objectives (National Collaborating Centre for Women's and Children's Health, 2008). It has been determined that breastfeeding itself promotes weight loss for the mother, decreases possibility of maternal progression to type 2 diabetes, reduces insulin resistance in mothers and decreases likelihood of obesity in the child. Children born to mothers who had poor glycemic control should undergo regular evaluations of height, weight and blood glucose concentration, as well as monitoring for appropriate physical activity and diet to minimize the likelihood of obesity (Elchalal, 2004).

5. Conclusion

The incidence of gestational diabetes is increasing and this pathological condition has strong association with adverse pregnancy outcomes. If untreated, gestational diabetes may lead to diverse complications, such as fetal hyperinsulinemia, increased weight at birth, higher rates of cesarian deliveries, shoulder dystocia, neonatal hypoglycemia, and it is also associated with concomitant preeclampsia in pregnant women. Therefore, given that gestational diabetes may have long-term pathological consequences for both mother and the child, it is important that it is recognized and correctly managed. Moreover, preconceptional screening and medical informing of women with diabetes type 1 or 2 would be significant in order to reduce risk to the fetus and mother connected to gestational diabetes. Treatment of gestational diabetes is aimed to maintain euglycemia and it should involve regular glucose monitoring, dietary modification, life style changes, exercise, and, when necessary, pharmacotherapy. Insulin therapy is the first choice of treatment, although glyburide and metformin could be indicated, too. In a long-term view, in order to prevent development of diabetes later in life, as well as different cardiovascular complications, an adequate education on lifestyle modifications should start in pregnancy and continue postpartum.

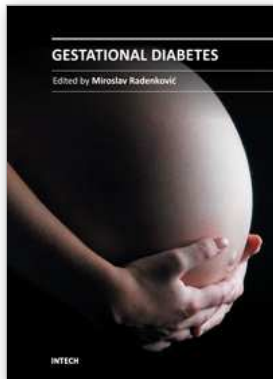
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Gestational Diabetes

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ISBN 978-953-307-581-5

Hard cover, 382 pages

Publisher InTech

Published online 02, November, 2011

Published in print edition November, 2011

Gestational diabetes mellitus is defined as hyperglycemia with onset or first recognition during pregnancy. The incidence of gestational diabetes is still increasing and this pathological condition has strong association with adverse pregnancy outcomes. Since gestational diabetes can have long-term pathological consequences for both mother and the child, it is important that it is promptly recognized and adequately managed. Treatment of gestational diabetes is aimed to maintain euglycemia and it should involve regular glucose monitoring, dietary modifications, life style changes, appropriate physical activity, and when necessary, pharmacotherapy. Adequate glycemic control throughout the pregnancy can notably reduce the occurrence of specific adverse perinatal and maternal outcomes. In a long-term prospect, in order to prevent development of diabetes later in life, as well to avoid associated complications, an adequate education on lifestyle modifications should start in pregnancy and continue postpartum.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Miroslav Radenković (2011). Treatment Considerations for Gestational Diabetes Mellitus and Long-Term Postpartum Options, Gestational Diabetes, Prof. Miroslav Radenkovic (Ed.), ISBN: 978-953-307-581-5, InTech, Available from: <http://www.intechopen.com/books/gestational-diabetes/treatment-considerations-for-gestational-diabetes-mellitus-and-long-term-postpartum-options>

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