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Management of diabetes and pregnancy – When to start and what pharmacological agent to choose?

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Gestational diabetes mellitus (GDM) complicates 3–15% of pregnancies depending upon the geographic location and ethnic groups, and its incidence is estimated to increase even further due to the increasing rates of obesity in the general population and the trend towards advanced maternal age in pregnancy. GDM is associated with adverse pregnancy outcome such as an increased rate of fetal macrosomia, neonatal metabolic disturbances, and maternal injuries. It has been shown that there is an inverse relation between maternal glycemic control and the risk of complications. When diet and exercise therapy fail in achieving good glycemic control, pharmacological intervention is warranted. This chapter deals with the evidence regarding the various pharmacological interventions for glycemic control in women with GDM, when to start, and what pharmacological agent to use.

Gestational diabetes, glycemic control, and adverse outcome

Although the association between gestational diabetes mellitus (GDM) and the risk of adverse pregnancy outcome is axiomatic, only in the last decade a positive relationship between the levels of maternal glycemia and perinatal morbidity and mortality was established. Langer et al. [1] have shown that in a matched control study of 555 gravidas with GDM diagnosed after 37 weeks who were

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compared with 1110 subjects treated for GDM and 1110 nondiabetic subjects, the composite adverse outcome was 59% for untreated, 18% for treated, and 11% for nondiabetic subjects. Moreover, a two- to fourfold increase in metabolic complications and macrosomia/large for gestational age was found in the untreated group with no difference between the nondiabetic and treated subjects [1]. Crowther et al. [2] randomly assigned 1000 women between 24 and 34 weeks of gestation who had GDM to receive dietary advice, blood glucose monitoring, and insulin therapy as needed (the intervention group) or routine care. The rate of serious perinatal complications was significantly lower among the infants of the 490 women in the intervention group than among the infants of the 510 women in the routine-care group (1% vs. 4%, $p = 0.01$) although higher rates of induction of labor and neonatal nursery admission were found in the intervention group [2]. Moreover, even in mild GDM (i.e., an abnormal result on an oral glucose tolerance test (OGTT) but a fasting glucose level <95 mg/dl), treatment was shown to reduce the risks of fetal overgrowth, shoulder dystocia, cesarean delivery, and hypertensive disorders [3]. Surprisingly, despite the fact that additional drug support with oral agents or insulin is administered in 20–60% of pregnancies compromised by GDM [4], scant evidence on glucose data and pregnancy outcome persists, as only a small percent of the thousands of published studies provided glycemic data on patients, and even in these studies, the majority did not provide the pregnancy outcome based on whether or not glycemic targets were reached, method of testing, and mean levels of glycemic data throughout pregnancy [5].

Although a thorough review regarding the effect of different glycemic targets and diabetes-related complications is beyond the scope of this chapter, before elaborating on various treatment modalities, it is prudent to understand the goals needed to be reached. Several authoritative bodies have recommended varying levels of glycemia that need to be targeted in patients with diabetes in pregnancy. The sources of these recommendations utilized the concept of isolated normality based on nondiabetic glucose profiles and are usually well-defined cutoff levels [6–8]. However, glucose values are best described as a continuous variable, and the risk to the fetus increases in direct relation to the increased level of maternal glycemia. For example, while maintaining mean blood glucose <100 mg/dl is associated with a similar risk of neonatal metabolic complications as the general population, levels >114 mg/dl increases the risk approximately twofold and >141 mg/dl over sevenfold compared to nondiabetic gravidas [4]. Thus, even if the optimal glycemic goals cannot be reached, it is important to keep on struggling as it would still minimize the risk of complications even if not abolishing it.

Oral antihyperglycemic and hypoglycemic agents

Several groups of oral agents for lowering blood glucose levels are currently available, and each group has a different set of pharmacological characteristics and mechanism of action allowing for the possibility of combining drug therapies.

Sulfonylureas

Sulfonylureas have been used in the treatment of type 2 diabetes since 1942. The major effect of this group of agents is to enhance insulin secretion from beta cells of the pancreas [9–13]. Moreover, sulfonylureas may further increase insulin levels by reducing hepatic clearance of the hormone, which is the main contributor to fasting hyperglycemia. They act by binding to specific receptors on the beta-cell membrane, closing potassium adenosine triphosphate (ATP) channels and opening calcium channels. The resulting increase in cytoplasmic calcium stimulates insulin release. A diminished glucose toxicity and improved insulin secretion following meals and, thus, reduction of postprandial hyperglycemia are achieved by enhanced insulin secretion. These drugs can also enhance peripheral tissue sensitivity to insulin [9,10]. The sulfonylureas influence insulin secretion in direct proportion to plasma glucose levels from 3.3 to 10 mmol/l (60–180 mg/dl). However, the stimulation of insulin secretion by sulfonylureas does not occur when the plasma glucose is <3.3 mmol/l (60 mg/dl) [14]. Thus, profound hypoglycemia is uncommon. The sulfonylureas act to facilitate rapid insulin secretion in response to nutritional intake, resulting in minimal to no lag time between the changes in plasma glucose and modification of the insulin secretory rate [15,16].