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Gestational Diabetogenesis

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The recognition of abnormal glucose levels and metabolism during pregnancy was first noted in 1824, when Heinrich Gottleib Bennewitz publicly defended his thesis for the degree of Doctor of Medicine at the University of Berlin. His one-line definition of the symptoms was "urine differing in quality and quantity from the normal… accompanied by unquenchable thirst and eventual wasting" [1]. The therapy at that time consisted of venous blood withdrawal and a high protein diet. The child died antepartum. "The baby was such robust and healthy, whom you would have thought Hercules had begotten". Baby's weight was 12 lbs.

Remarkable progress has been made over the past 2 centuries on pathogenesis, diagnosis and treatment of gestational diabetes.

The definition of Gestational Diabetes Mellitus (GDM) as any degree of glucose intolerance with onset or first recognition during pregnancy is largely accepted. According to the World Health Organization, diabetes may be the most frequent metabolic pathological condition influencing the fate of a pregnant woman and her fetus. Gestational diabetes complicates 2-10% of all pregnancies. Women, who have had gestational diabetes, have a 35% to 60% chance of developing diabetes in the next 10-20 years [2].

Pregnancy state leads to increased demand on pancreatic insulin secretion, as well as tissue insulin resistance.

Normal pregnancy is characterized by accelerated starvation, which is manifested by an earlier shift from carbohydrate to fat metabolism in a fasting state, and facilitated glucose metabolism in a fed state. Both processes are more prominent during late pregnancy. Glucose uptake by the fetus is approximately 6 mg/kg/min. Maternal hepatic glucose production needs to increase by 14% in order to provide continuous energy supply for the fetus [3].

Fasting insulin levels are similar in a pregnant and non-pregnant state, but a 3-4 fold increase in insulin secretion is required in response to glucose load, in order to maintain an equivalent glucose disposal rate [4].

Performing hyperinsulinemic euglycemic clamp in normal pregnancy, Catalano et al. [5] showed 56% decrease in insulin sensitivity from before conception through 34 to 36 weeks gestation.

Metabolic abnormalities which predispose to the development of gestational diabetes include defects in insulin action, together with impaired compensation for insulin resistance with advancing gestation. Consequently, this results in significantly higher plasma glucose levels in women with GDM at all-time points during OGTT (Oral Glucose Tolerance Test), compared to those with non-GDM pregnancies [6].

A decrease in both the 1st and 2nd phases of insulin secretion has been demonstrated in pregnancies complicated by GDM [7]. In most cases, GDM represents chronic β-cell dysfunction that is only detected during pregnancy.

Pregnancy complicated by GDM can affect both the mother and the fetus. Risks for the mother include progression of pre-existing diabetes complications, spontaneous abortion, pre-eclampsia, hydramnios, macrosomia, operative delivery and stillbirth. Risks for the fetus consist of intra-uterine growth retardation, macrosomia and neonatal hypoglycemia. Therefore, GDM risk assessment should be performed at the first prenatal visit. Until recently, an average at risk pregnant woman were screened by the two step approach, with the use of 1 hour 50 gram glucose load followed by a 3 hour 100 gram OGTT, (Oral Glucose Tolerance Test), if the first test was abnormal.

In 2010, IADPSG (The International Association of Diabetes and Pregnancy Study Groups) issued new guidelines for the strategy of detection and diagnosis of hyperglycemic disorders during pregnancy [8]. Fasting plasma glucose, hemoglobin A1C level, or random plasma glucose levels should be measured in most women during the first prenatal visit. If fasting plasma glucose is lower than 92 mg/dl, OGTT should be performed at 24-28 weeks of gestation, after an overnight fast by measuring blood glucose levels at 2 hour post 75 grams of glucose load. These guidelines are based on the largest study on Hyperglycemia and Adverse Pregnancy Outcomes (HAPO), which involved over 25,000 women from 15 medical centers in 9 countries, assessing the effect of hyperglycemia on both maternal and fetal pregnancy outcomes [9]. The study results revealed continuous association of maternal glucose levels with increased birth weight, cord serum c-peptide level, neonatal hypoglycemia and the need for a C-section.

New diagnostic criteria of a 75 gram OGTT was established based on the results of the HAPO study, with the use of a pre-defined odd ratio of 1.75 for the development of the above complications:fasting plasma glucose of 92 mg/dl, 1 hour plasma glucose of 180 mg/dl and 2 hour plasma glucose of 153 mg/dl. One or more of these values must be equaled or exceeding, for the diagnosis of GDM [9].

Historically, insulin is considered the gold standard therapy for GDM. Until recently, NPH insulin was the only intermediate acting insulin approved for use during pregnancy. In April, 2012, Levemir (Detemir) received FDA approval for a pregnancy category B administration, indicating that Levemir, when used in pregnant women with diabetes, did not increase the risk of harm to the fetus. Considering the peak of action of NPH insulin, use of Levemir offers an option of peak less insulin, especially in women predisposed to nocturnal hypoglycemia, which has been shown in a recent study [10].

There is limited research on the safety of insulin analogs during pregnancy. There are a number of retrospective and prospective studies evaluating the safety and efficacy of Humalog and Novolog therapy in pregnancy, which up to date showed no statistically significant difference in fetal and maternal outcomes, and even showed a tendency towards decreased rates of hypoglycemia. Recent systematic review and meta-analysis of Humalog versus Regular insulin identified a higher rate of large-for-gestational-age infants (>90th percentile), despite

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similar HbA_{1c} levels in the Humalog group (relative risk, 1.38 (95% CI, 1.14-1.16) [11].

Insulin use in GDM requires extensive teaching, monitoring, which frequently causes anxiety and inconvenience leading to noncompliance. Therefore, the ability to use oral medications is a very plausible opportunity. Unfortunately, the safety data on the use of oral hypoglycemic agents during pregnancy is very sparse and requires further research. Glyburide, one of the most studied oral agents, showed only minimal crossing of the placenta. Elliott et al. [12] compared glyburide with insulin in 404 women with GDM, and demonstrated no difference in perinatal outcomes between the groups; Glyburide was not detected in the cord serum. Several subsequent studies showed promising results of the treatment with Glyburide, which lead to a growing acceptance of its use as a primary therapy for GDM.

In conclusion, the unique feature of GDM is its identification during pregnancy, a period when insulin resistance is universal, provides an exclusive opportunity to identify young women at risk for diabetes, to study the pathogenesis of hyperglycemia, and to intervene at its very early stages.

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