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Gestational diabetes mellitus

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There is a huge scientific interest with a lot of publications in the last decade dealing with the hyperglycemia in pregnancy because of increased risk for the mother and fetus accompanying this condition. The hyperglycemia in pregnancy can be classified 1. as diabetes in pregnancy and 2. as gestational diabetes mellitus (FIGO 2015). The last few years is made clear that the excellent metabolic control during pregnancy leads to less perinatal and future complications for mother and fetus. The diabetes in pregnancy can be divided as diabetes diagnosed before pregnancy (Type 1 and Type 2) and as diabetes diagnosed for the first time during pregnancy (Type 1 and Type 2). The gestational diabetes mellitus was earlier defined as any glucose intolerance beginning or first diagnosed during pregnancy. The current definition, based on recent studies, includes the hyperglycemia state diagnosed in the second and more often in the third trimester of pregnancy which does not fulfill the criteria for overt, classical diabetes but coincides with the state of prodiabetes.

In every pregnancy there is a state of insulin resistance due to increased levels of hormones counteracting the insulin action (human chorionic goanadotropin from synciotblasts and later human placental lactogen, prolactin, progesterone and estradiol). The levels of these hormones become higher with the progression of the pregnancy leading to further increase of insulin resistance. If the maternal pancreas can compensate with increased insulin production the glucose metabolism remains normal during the whole pregnancy but, if there is also an insulin secretory(b-cell) defect, the insulin production can not increase appropriately and hyperglycemia evolves. In normal pregnancies during the OGTT, according to many studies, the fasting glucose is about 71±8 mg/dl, the one-hour PP value is 109±13 and the 2hours PP is 99±10 mg/dl. If we add 1SD to these values the 1h PP the suggested target is 122 and the 2h PP is 110 mg/dl respectively. There was a lot of disagreement among the various authors and diabetes associations and many modifications in the last 55 years about which OGTT should be used to define the gestational diabetes and predict better the risk for adverse pregnancy outcome. A 1,2 and 3hours OGTT have been used with the administration of 50, 75 or 100 gr of glucose. In 2008 the HAPO (Hyperglycemia and Adverse Pregnancy Outcome)

study was published. 25.000 pregnancies with mild glucose intolerance were studied with a 2h, 0' 1 and 2h glucose values, 75 gr OGTT performed between 24 and 32 gestational weeks. Women with FPG>105 and 2h PP>200 mg/dl were excluded from the study. The primary end points were BW>90th percentile, umbilical C-peptide>90th percentile, neonatal clinical hypoglycemia and caesarean section percentage. There was an absolute linear correlation between the pregnant women glucose values with these primary end points at values lower than those seen in classical diabetes. Similar results were observed in the ACHOIS and MFMU (Maternal and Fetal Pregnancy Units, trials. According to these trials in 2010 the International Association of Diabetes and Pregnancy Study Groups (IADPSG) Recommendations of Hyperglycemia in Pregmancy (Consensus) were published with gestational diabetes diagnosed if the following values were met or exceeded: Fasting 92 mg/dl or 5,1 mmol/l, one hour 180 mg/dl or 10 mmol/L and 2 hours 153 mg/dL or 8,5 mmol/L in an OGTT with 75 g of glucose at 24-28 pregnancy weeks (one-step strategy). One abnormal value is sufficient for the diagnosis of GDM to be made. The two-steps strategy can also be used with 50 g of glucose (non fasting) given as screening test and if the one hour glucose value is >140 mg/dL or 7,8 mg/L the 3-hours OGTT with 100g of glucose (fasting) is performed. The diagnosis of gestational diabetes is made if 2 of the 4 glucose values in fasting, 60', 120' and 180' meet or exceed the following: Fasting 92 mg/dL or 5,1 mmol/L, 1h 180 mg/dL or 10 mmol/L, 2h 155 mg/dL or 8,6 mmol/L and 3h 140 mg/dL or 1,8 mmol/L. (ADA 2016). The Hellenic Diabetes Association recommends that all the pregnant women must be screened fasting in the first visit and if the value is <92 perform a 2hs OGTT with 75 g glucose at 24-28 pregnancy week. If the glucose value is >92 and <126 there is gestational diabetes and if it is ≥126 or the 2h PP is ≥ 200 mg/dL there is overt type 2 DM.

Risk factors for gestational diabetes are among others history of IGT or GDM, age > 25 years, BMI>30 with excessive weight gain, family history of DM, history of POS or pregnancy with bad outcome, presence of metabolic syndrome, multiple pregnancy and some nationalities. Some of these are modifiable and some not modifiable. The relative risk of neonatal birth weight above the 90th percentile is 5,35 if there is GDM and the mother is obese compared with normal glucose tolerance and normal mother's weight. The glycemic targets during pregnancy in order to prevent mother and fetal complications according to experts' opinion in pregnant with GDM are: preprandial (premeal) ≤90 mg/d (5 mmol/L)l, 1-hour postprandial ≤ 120 mg/d (6,7 mmol/L)l and HbA1c ≤ 5%.The same targets are valid for women with preexisting type 1 or type 2 DM with the exception of HBA1c which must be≤6%).

75% of women with GDM can be controlled with life style modifications alone (diet and exercise). The diet must not contain less than 1600-1800 Kcal/24 h. The carbohydrates must be≈35-45% of the total caloric intake (no easily absorbable sugars), the protein 20-25% and the fats 30-40%. The meals must be small and frequent to avoid ketosis and in obese women medium caloric restriction (25 Kcal/Kg/day) is recommended. The exercise sessions must be either 30 min of aerobic exercise (e.g. brisk walking) in 24hs in exercise capable women or upper limbs exercise in sitting position lasting at least 10 min (after meals). If the life style changes are not sufficient for adequate glucose control drug therapy must be initiated. Insulin, glibencamide (glyburid) and metformin are safe and effective therapy for achieving desirable glycemic control. However there is no long term sufficient evidence for oral antidiabetic therapy and insulin is preferred. According to a metaanalysis glibenclamide is clearly inferior both to metformin and insulin. Metformin does not seem to increase risk for fetal malformations while half of the patients on metformin will finally require insulin. Glibenclamide caused more neonatal ICU admissions, more cases with respiratory distress, hypoglycemia, birth injury and large for gestational age infants compared with insulin. Insulin must be initiated if FBG is >95 mg/dL, 1-hour postprandial >140 or there is fetal macrosomia in ultrasound (abdominal circumference >75th percentile). Insulins considered safe in pregnancy are these with intermediate duration of action NPH and levemir, the human regular insulin and the preferred rapid-acting analogs aspart and lispro (category B). Insulin glargine although frequently prescribed in pregnancy has not been definitely established as safe (category C).

Women with GDM must be followed every two

weeks both by the obstetrician and the diabetes specialist, must have an initial HBA1c in order to exclude preexisting DM, must measure their blood glucose 4-6 times daily (before and 1-hour after meals) and have an ultrasound every 2-3 weeks. Continuous glucose monitoring with CGMS in GDM has shown benefits in many cases. This helps when there is inability to achieve the desired glycemic control with SMBG alone as it identifies undetected glucose excursions. It can lead to reduced birth weight and decreased risk for infant macrosomia by improving the glycemic control in the third trimester. The recommended mothers' weight gain during pregnancy is related to pregestational BMI. A woman with pregestational BMI>30 must not gain more than 5-9 Kg while one with BMI <18 is allowed to gain 12-18 Kg.

The complications in mothers with GDM include preeclampsia, hypertension in pregnancy, mother's birth trauma and increased risk for caesarean section. The long term mother's complications include the increased risk for future development of DM type 2 (X5 in 5 years, X10 in 10 years) and increased risk for future cardiovascular disease. It is recommended that the mother is monitored for dysglycemia at regular intervals after delivery: 1-3 days – FBG, 2-3 months – OGTT, 1year – OGTT, every year – FBG, every 3 years and before next pregnancy – OGTT.

The fetal complications in GDM include sudden intrauterine (after 38wk) and perinatal death, macrosomia, fetal trauma or asphyxia, shoulder dystocia, neonate respiratory distress syndrome (RDS), polyhyramnio, fetal hypertrophic cardiomyopathy and metabolic abnormalities as hypoglycemia, jaundice, polycythemia and hypocalcemia. Long-term offspring's complications include increased risk for obesity, prediabetes and type 2 diabetes and both systolic and diastolic hypertension during their adolescence and adulthood. The GDM is no indication for caesarean section by itself, lactation is desirable while women on insulin usually don't need it during labor and is usually stopped after this. Lactating women even for 6-9 weeks after delivery had lower frequency of prediabetes and type 2 diabetes compared with the non lactating.

It is concluded that there is a need for search for preexisting DM from the first visit, the prevalence of GDM is increased due to world obesity pandemic, the GDM is pathophysiologically correlated to increased insulin resistance, there is a direct and linear correlation of hyperglycemia with adverse perinatal outcome, GDM must be searched and treated vigorously, life style and insulin are the appropriate treatment options and the women with GDM are at increased risk for future development of DM type 2 and CVD.