Current strategy for detection and diagnosis of hyperglycemic disorders in pregnancy

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Summary

Gestational diabetes mellitus (GDM) is a metabolic alteration frequently found in pregnant women.
In women with GDM, failure of pancreatic beta-cells to adapt the production of insulin at the increased metabolic demand in pregnancy, results in a inadequate insulin response, with consequent hyperglycemia.
The criteria currently used for the diagnosis of GDM are too restrictive as some author suggested that different degrees of hyperglycemia, even though not diagnostic for diabetes, increase the risks of adverse perinatal outcomes (large for gestational age (LGA), higher rate of cesarean section, neonatal hypoglycemia, respiratory distress, perinatal mortality).
The objective of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study was to clarify the associations of levels of maternal glucose, lower than those diagnostic of diabetes, with perinatal outcome, defining a new overall strategy recommended for detection and diagnosis of hyperglycemic disorders in pregnancy.

Key Words: gestational diabetes mellitus (GDM); HAPO study; hyperglycemic disorders; pregnancy.

Introduction

Gestational diabetes mellitus (GDM), a common medical complication of pregnancy, is defined as "any degree of glucose intolerance with onset or first recognition during pregnancy" (1,2). Gestational diabetes is a metabolic alteration frequently found, but its true prevalence remains a matter of debate ranging between 2% and 9%, with highs of around 14% of all pregnancies. Higher prevalence (14%) is found in the U.S.A., in the ethnic groups in American Indians, Asians, Hispanics and African-Americans who are at higher risk of gestational diabetes than Caucasians (3). The increase of gestational diabetes in these ethnic groups is attributed, in addition to generic characteristics, at the rapid change of lifestyle, dietary habits and a sharp reduction of physical activity of these populations, once got in touch with the world industrialized.
From the standpoint of pathogenesis, gestational diabetes has many common features with type 2 diabetes mellitus and may be considered as a set of conditions with different pathogenetic moments.
The result is, however, a production of insuline (unlike the diabetes mellitus type 1) inadequate to meet the requirements for the maintenance of normal tissue glucose metabolism in pregnancy.
In the physiological pregnancy, the glucose homeostasis is maintained, despite the development of some degree of insulin resistance, through a concomitant compensatory increase in insulin secretion. In women with GDM the presence of "chronic" insulin resistance before the pregnancy and/or the failure of pancreatic beta-cells to adapt the production of insulin at the increased metabolic demand, results in a inadequate insulin response, with consequent hyperglycemia (3).
There is consensus that diabetes during pregnancy, whether symptomatic or not, is associated with significant risk of adverse perinatal outcome. Some have attributed risks of adverse outcomes associated with GDM, such as birth weight that is large for gestational age (LGA), excess fetal adiposity, and higher rate of cesarean section, to confounding characteristics, such as obesity, more advanced maternal age, or other medical complications, rather than glucose intolerance (4, 5). Others neonatal complications of GDM are: neonatal hypoglycemia, respiratory distress, perinatal mortality.
There are specific risk factors for the GDM under which the population is divided into the following categories (6):

- **LOW RISK**
  If all the following characteristics are evident:
  1. Member of an ethnic group with low prevalence of GDM;
  2. No family history of diabetes mellitus;
  3. Obstetric history without adverse outcomes;
  4. Aged under 25 years;
  5. Normal weight;
  6. Normal birth weight.
- **MIDDLE RISK**
  For women with intermediate characteristics between the LOW and HIGH RISK.
- **HIGH RISK**

If there are one or more of the following factors:

1. Family history of diabetes mellitus in first degree family;
2. Previous detection of glucose intolerance;
3. Fetal macrosomia in previous pregnancies;
4. Obesity;
5. Pronounced glycosuria in the current pregnancy.

Some suggest that criteria currently used for the diagnosis of GDM are too restrictive and that also lesser degrees of hyperglycemia increase risks of adverse perinatal outcomes (7, 8). On the contrary, others believe that systematic efforts to identify GDM should be stopped unless data become available to link significant morbidities to specific degrees of glucose intolerance (9).

Lack of international uniformity in the approach to ascertainment and diagnosis of GDM has been a major hurdle (2).

The HAPO study

In June, 11-12th 2008, the International Association of Diabetes and Pregnancy Study Groups (**IADPSG**) sponsored an International Workshop-Conference on Gestational Diabetes Diagnosis and Classification in Pasadena, California. More than 225 conferees from 40 countries reviewed published results of the Hyperglycemia and Adverse Pregnancy Outcome (**HAPO**) study, additional unpublished HAPO study findings, and results of other works that examined associations of maternal glycemia with perinatal and long-term outcomes in offspring.

HAPO study results (10, 11) were considered in depth in arriving at the recommendations for diagnosis of GDM. Recommendations for detection of overt diabetes during pregnancy are based on the opinions of the IADPSG Consensus Panel members.

The objective of the HAPO study was to clarify associations of levels of maternal glucose lower than those diagnostic of diabetes with perinatal outcome (10, 12). This was accomplished by performing a 75-g oral glucose tolerance test (OGTT) with three measures of maternal glucose (fasting plasma glucose [FPG], 1-h, and 2-h post–75-g load) on a heterogeneous, multinational, multicultural, ethnically diverse cohort of ~25,000 women in the third trimester of gestation (24-28 gestazional week). HAPO data show strong linear associations of risks for >90th percentiles of birth weight, cord C-peptide, and percent body fat with each of three measures of maternal glucose.

Analyzing these data, the diagnostic threshold obtained are respectively:

- **FPG** 5.1mmol/l (**92 mg/dl**);
- **1-h plasma glucose** 10.0 mmol/l (**180 mg/dl**);
- **2-h plasma glucose** 8.5mmol/l (**153 mg/dl**).

At least one of these thresholds must be equaled or exceeded to make a diagnosis of GDM.

The classical definition on GDM has defined the condition as "any degree of glucose intolerance with onset or first recognition during pregnancy" (1, 2). This definition has applied whether or not insulin is used for treatment or hyperglycemia persists after pregnancy. The possibility that unrecognized glucose intolerance antedated the pregnancy is not excluded. The need to identify these women and address perinatal risks that may be particular to their greater degree of hyperglycemia is becoming more important. The issue of classification of women with likely pre-pregnancy diabetes (**overt diabetes**) first noted during pregnancy was addressed via presentations by experienced clinicians/researchers accompanied by interactive discussion. Several arguments were made for identifying as a distinct group women with overt diabetes: increased risk of congenital anomalies in offspring (13); risk of diabetes complications (nephropathy and retinopathy) requiring treatment during pregnancy (14); need for rapid treatment and close follow-up during pregnancy to ensure prompt restoration of normal glycemia (15,16); need to ensure confirmation and appropriate treatment of diabetes after pregnancy. It is desirable to detect overt diabetes in pregnancy as early as possible to provide an opportunity to optimize pregnancy outcome. However, there is variability in time of enrollment for prenatal care beyond the control of health care providers.

The overall strategy recommended for detection and diagnosis of hyperglycemic disorders in pregnancy consists of two discrete phases. The first is detection of women with overt diabetes not previously diagnosed or treated outside of pregnancy by a single laboratory measure of fasting glucose (FPG, random plasma glucose). Universal early testing in populations with a high prevalence of type 2 diabetes is recommended during the first prenatal visit, especially if metabolic testing in this age-group is not commonly performed outside of pregnancy.

- If results, at first trimester, indicate **overt diabetes** with fasting plasma glucose ≥ **7.0 mmol/l (126 mg/dl)**, treatment and follow-up as for preexisting diabetes.
- If results are not diagnostic of overt diabetes, with fasting plasma glucose ≥ **5.1 mmol/l (92 mg/dl) but < 7.0 mmol/l (126 mg/dl), diagnose of GDM**.
- If results are not diagnostic of overt diabetes with fasting plasma glucose **< 5.1 mmol/l (92 mg/dl)**, plan **test for GDM from 24 to 28 weeks' gestation with a 75-g OGTT**.

The second phase is a 75-g OGTT at 24–28 weeks' gestation in all women not previously found to have overt diabetes or GDM.

Furthermore we must remembered that a pregnant woman suffering by GDM, will be subject to increased risk of developing type 2 diabetes mellitus in the first five years following the pregnancy. The glucose tolerance should be revaluated after delivery: is advisable to perform a revaluation after six weeks post-partum or after lactation, using standard OGTT. If a decreased glucose tolerance or altered fasting glucose are diagnosed, the revaluation will be conducted annually; where the glucose tolerance were normal, the revaluation should be executed at intervals not exceeding three years.

Conclusion

The HAPO study was a basic epidemiological investigation that for the first time conclusively identified strong continuous associations of maternal glucose levels below those diagnostic of diabetes with several perinatal outcomes. It was not a clinical trial, but two randomized controlled trials of treatment of mild GDM have been carried out successfully in participants with glucose values that overlap with the thresholds recommended in this report. However, it is likely that additional well-designed randomized controlled trials and other clinical studies will be needed to determine:

1) cost-effective therapeutic strategies for treatment of GDM diagnosed by the IADPSG Consensus Panel-recommended criteria;
2) optimal glycemic treatment targets;
3) appropriate follow-up in mothers to determine risks for later development of diabetes, other metabolic disorders, or cardiovascular risk factors;
4) follow-up of children to assess potential associations of maternal glycemia with long-term risks of obesity, altered glucose metabolism, and cardiovascular risk factors.

References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus (Position Statement). Diabetes Care 2009.
2. Metzger BE, Coustan DR. Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus: the organizing committee. Diabetes Care 1998.
3. Gabbe SG et al. Obstetrics: Normal and Problem Pregnancies, 4th ed. Churchill Livingstone, 2001.
4. Jarrett RJ. Reflections on gestational diabetes. Lancet 1981.
5. Spellacy WN, Miller S, Winegar A, Peterson PQ. Macrosomia: maternal characteristics and infant complications. Obstet Gynecol 1985.
6. Reece A, Coustan D. Il diabete mellito in gravidanza. Guidotti, 1998.
7. Jensen DM, Damm P, Sørensen B, Mølsted-Pedersen L, Westergaard JG, Klebe J, Beck-Nielsen H. Clinical impact of mild carbohydrate intolerance in pregnancy: a study of 2904 nondiabetic Danish women with risk factors for gestational diabetes. Am J Obstet Gynecol 2001.
8. Ferrara A, Weiss NS, Hedderson MM, Quesenberry CP Jr, Selby JV, Ergas IJ, Peng T, Escobar GJ, Pettitt DJ, Sacks DA. Pregnancy plasma glucose levels exceeding the American Diabetes Association thresholds, but below the National Diabetes Data Group thresholds for gestational diabetes mellitus, are related to the risk of neonatal macrosomia, hypoglycaemia and hyperbilirubinaemia. Diabetologia 2007.
9. Hunter DJS, Keirse MJNC. Gestational diabetes in effective care. In Pregnancy and Childbirth. Chalmers I, Enkin M, Kierse M, Eds. New York, Oxford University Press, 1989.
10. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, Oats JJ, Persson B, Rogers MS, Sacks DA, Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008.
11. HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. Diabetes 2009.
12. HAPO Study Cooperative Research Group. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. Int J Gynaecol Obstet 2002.
13. Schaefer UM, Songster G, Xiang A, Berkowitz K, Buchanan TA, Kjos SL. Congenital malformations in offspring of women with hyperglycemia first detected during pregnancy. Am J Obstet Gynecol 1997.
14. Omori Y, Jovanovic L. Proposal for the reconsideration of the definition of gestational diabetes. Diabetes Care 2005.
15. Bartha JL, Martinez-Del-Fresno P, Comino-Delgado R. Gestational diabetes mellitus diagnosed during early pregnancy. Am J Obstet Gynecol 2000.
16. Maegawa Y, Sugiyama T, Kusaka H, Mitao M, Toyoda N. Screening tests for gestational diabetes in Japan in the 1st and 2nd trimester of pregnancy. Diabetes Res Clin Pract 2003.