Early recognition of gestational diabetes (Introduction of new guidelines and practice) – how should the routines be?

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Introduction

Diabetes in pregnant women may be pregestational, where the diabetes, type 1 or type 2 was diagnosed before pregnancy, or hyperglycemia can be first recognised during the pregnancy that comprise two distinct categories - gestational diabetes mellitus (GDM) and previously unrecognised prepregnancy diabetes, so called »overt« diabetes (1). Women who are in poor glycemic control during the period of fetal organogenesis, which is nearly complete by twelfth week postconception, have a high incidence of spontaneous abortion and fetuses with congenital anomalies. The risk increase exponentially with increasing glycosylated haemoglobin (HbA1c). On the other hand, the malformation rates are similar to the background population of around 2% when the early pregnancy HbA1c is within normal range (2). Therefore, importance of preconceptional evaluation and counselling of women with pregestational diabetes mellitus cannot be overstated. Later in pregnancy, poor glycemic control increases the risk of macrosomia and its sequelae by two to four times (3,4,5). Additionally, perinatal mortality rates (stillbirths and first-week neonatal deaths) among women who are diabetic remain approximately two to four time higher as those observed in the nondiabetic population, and perinatal morbidity (neonatal hypoglycemia, respiratory distress, hyperbilirubinemia and jaundice, hypocalcaemia, hypomagnesaemia, polycythemia, transient hypertrophic cardiomyopathy with congestive cardiac failure) is higher as well (2,5). In addition to fetal complications, pregnancy in women with pregestational diabetes can adversely influence maternal health. In particular, women can suffer from treatment-induced hypoglycemia and worsening of pre-existing micro- and macro-vascular complications, such are retinopathy, nephropathy, neuropathy and cardiovascular disease (2). Gestational hypertension and pre-eclampsia are two to twelve times more common (3,4,5). Finally, the long-term impact on offspring of exposure to hyperglycemia in utero result in a greater risk of obesity, metabolic syndrome and type 2 diabetes later in life, due to epigenetic modifications of gene expression (2). Early recognition of overt diabetes in pre-pregnancy unrecognized type 2 diabetic women, and recognition of gestational diabetes with undelayed achievement of normoglycemia is therefore crucial for optimizing maternal and fetal outcomes in all women with hyperglycaemia during pregnancy, regardless of the type of diabetes.

Diagnosis of hyperglycemia during pregnancy

Before the International Association of Diabetes and Pregnancy Study Group (IADPSG) recommendations have been launched, the absence of a universally accepted "gold standard" for the diagnosis of GDM has resulted in a variety of recommended diagnostic thresholds that have been endorsed by different organisations in their guidelines. None of those diagnostic criteria were based on fetal or maternal outcomes of the pregnancy. To overcome this shortage the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study was designed. The study involved 25505 pregnant women from 15 centres in nine countries. It was the first study, designed to clarify risks of fetal and maternal adverse outcomes associated with degrees of maternal glucose intolerance less severe than those with overt diabetes during pregnancy. Women were tested using 75-g oral glucose tolerance test (OGTT) at 24-32 weeks. The study found a continuous positive association with increasing glucose levels and birth weight >90th percentile, cord C-peptide >90th percentile, primary Cesarean section and neonatal hypoglycemia. The study also found positive associations between increas-

ing plasma glucose levels and each of the five secondary outcomes examined: premature delivery, shoulder dystocia or birth injury, intensive neonatal care, hyperbilirubinemia and preeclampsia. The associations were strongest for birth weight and blood serum C-peptide levels (6). Results from the HAPO study was the basis for IADPSG recommendations launched in 2010.

Historically, the term "gestational diabetes" was used to define women with onset or first recognition of abnormal glucose tolerance during pregnancy. After the IADPSG consensus it is prudent to distinguish women with probable pre-existing diabetes that is first recognised during pregnancy – »overt diabetes« from those with transient hyperglycemia due to pregnancy related insulin resistance – »GDM«. The rationale for this recommendation is based on the fact that an increasing proportion of young women have as yet overt but unrecognized type 2 diabetes, due to the increasing prevalence of obesity, and lack of routine glucose screening/testing in this age group. Beside this, nowadays women decide for pregnancy later in life, what is inevitably related to a higher incidence of diabetes type 2. Identifying overt diabetes early in pregnancy as a distinct group is important because these women are at increased risk of congenital anomalies in offspring, are at risk of diabetes complications (nephropathy and retinopathy), and require rapid treatment of hyperglycaemia during pregnancy to ensure prompt restoration of normal glycemia and close follow-up during pregnancy. Early identification of overt diabetes and treatment of hyperglycemia may reduce these risks and provide an opportunity to optimize pregnancy outcome (1).

The overall strategy recommended by the IADPSG Consensus Panel for detection and diagnosis of hyperglycemic disorders in pregnancy include two discrete phases (Figure 1). The purpose of the first phase is detection of women with overt diabetes not previously diagnosed or treated outside of pregnancy. Detection and diagnosis of overt diabetes during pregnancy should be made during the initial visit for prenatal care. Universal early testing in populations with a high prevalence of type 2 diabetes is recommended by some organisations (1,7). In health care systems not deciding for universal testing, screening for undiagnosed type 2 have to be performed in those with risk factors, such as listed in Table 1 (8,9). The diagnosis of overt diabetes is confirmed using standard diagnostic criteria: fasting plasma glucose $\geq$ 7,0 mmol/L or HbA1c $\geq$ 6,5% or random plasma glucose $\geq$ 11,1 mmol/L plus confirmation (Table 2). If results indicate overt diabetes treatment and follow-up as for pre-existing diabetes is mandatory. If results are not diagnostic of overt diabetes and fasting plasma glucose is $\geq$5,1 mmol/l (92 mg/dl) but <7,0 mmol/l (126 mg/dl), diagnose immediately as GDM. In all other women, not found to have overt diabetes or GDM at early testing, the second phase is one step 75-g OGTT performed at 24–28 weeks' gestation. According to IADPSG recommendations GDM should be diagnosed if one or more values from a 75-g OGTT equal or exceed those listed in Table 3 (1). As a result of IADPSG consensus, many organizations have published new recommendations for screening and diagnosis of diabetes in pregnancy. World Health Organisation (WHO) (10) and Endocrine society (7), adopt IADPSG criteria (75-g OGTT as one step approach), while American Diabetes Association (ADA) (8) and Canadian Diabetes Association (9) allow using two approaches (75-g OGTT as one step approach or 50-g OGTT followed with confirmation testing using either 100-g OGTT in USA or 75-g OGTT in Canada as two step approach), NICE guidelines are in development.

However since there is a continuous risk of adverse outcomes with increasing glycemia in HAPO study, diagnostic thresholds are somewhat arbitrary. The IADPSG Consensus Panel decided to define diagnostic values listed in Table 3 on the basis of an odds ratio of 1,75 for adverse neonatal outcomes. Based on HAPO study population the total incidence of GDM would be around 17,8% of all pregnant women (1). The one step approach proposed by the IADPSG, is anticipated to significantly increase the prevalence of GDM (from 5-6% to ~15-20%), primarily because the recommended glucose cut-off values for GDM correspond to those proposed by IADPSG are lower than those recommended by earlier guidelines, and because the

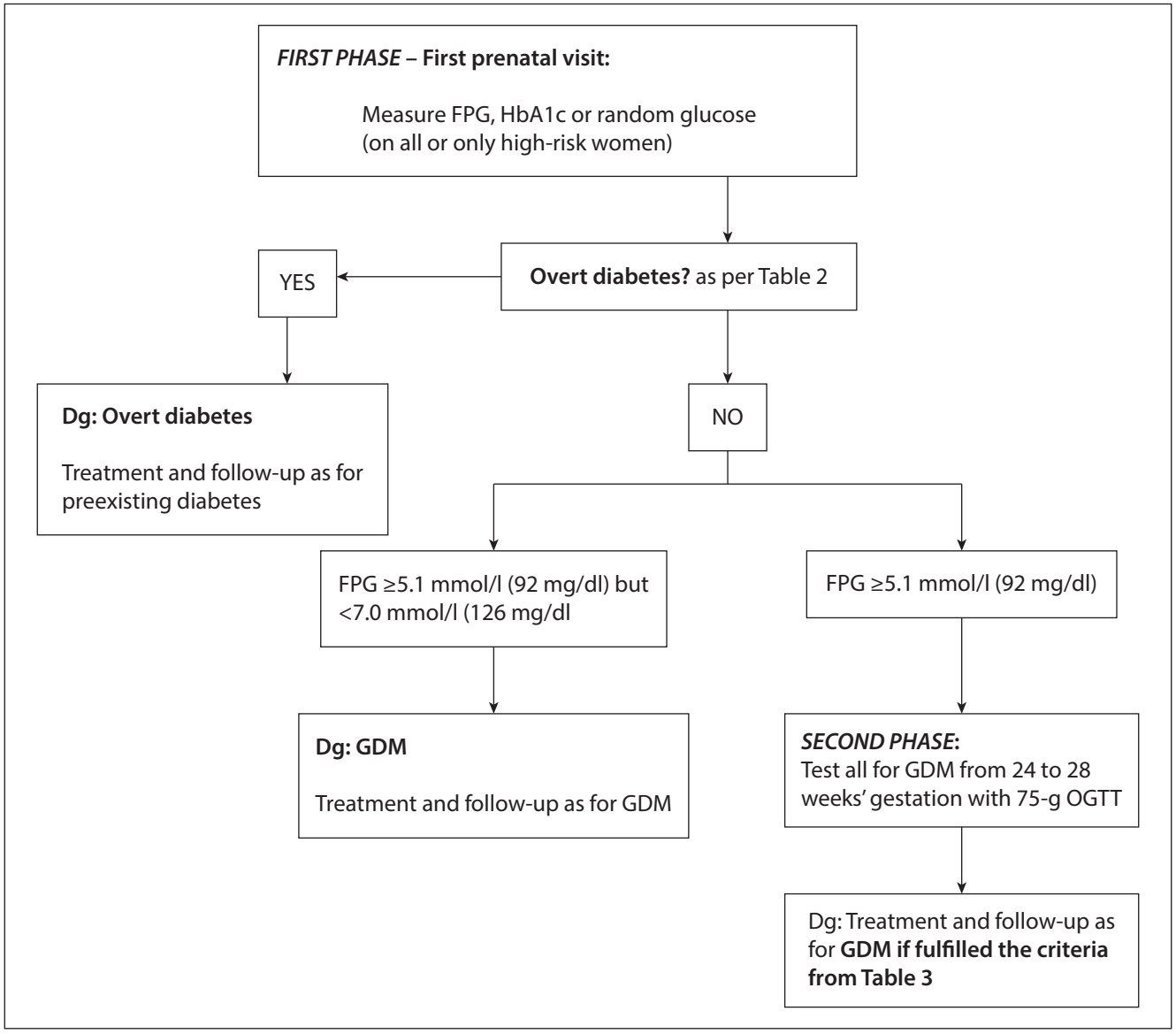

Figure 1. Strategy for the detection and diagnosis of hyperglycemic disorders in pregnancy.

Table 1. Risk factors for hyperglycemia during pregnancy (from a reference 8).

Testing should be considered in all women who are overweight (BMI ≥25 kg/m2) and have additional risk factors:
1. physical inactivity
2. first-degree relative with diabetes
3. high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian,American, Pacific Islander)
4. women who delivered a baby weighing 4,1 kg or were diagnosed with GDM
5. hypertension (140/90 mmHg or on therapy for hypertension)
6. HDL cholesterol level <0.90 mmol/L and/or a triglyceride level >2.82 mmol/L
7. women with polycystic ovarian syndrome
8. A1c ≥5.7%, IGT, or IFG on previous testing
9. other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
10. history of CVD

BMI – Body mass index, IGT – impaired glucose tolerance, IFG – impaired fasting glucose, CVD – cardiovascular disease

Table 2. Threshold values for diagnosis of overt diabetes in pregnancy (from a reference 1). Decision to perform blood testing for evaluation of glycemia on all pregnant women or only on women with characteristics indicating a high risk for diabetes is to be made on the basis of the background frequency of abnormal glucose metabolism in the population and on local circumstances.

Measure of glycemia	Consensus threshold
FPG	≥7.0 mmol/l (126 mg/dl)
A1c	≥6.5% (DCCT/UKPDS standardized)
Random plasma glucose	≥11.1 mmol/l (200 mg/dl) + confirmation

Table 3. Threshold values for diagnosis of GDM (from a reference 1).

Glucose measure	Glucose concentration threshold*	
	mmol/l	mg/dl
FPG	5.1	92
1-h plasma glucose	10.0	180
2-h plasma glucose	8.5	153

***** One or more of these values from a 75-g OGTT must be equaled or exceeded for the diagnosis of GDM.

only one abnormal value, not two, is sufficient to make the diagnosis (8,10). Increased prevalence of GDM would have significant impact on the costs, medical infrastructure capacity, and potential for increased "medicalisation" of pregnancies previously categorised as normal (8). Nevertheless, IADPSG diagnostic criteria for the treatment of GDM seem to be reasonable. Two randomized controlled trials, Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) and a multicenter, randomized trial of treatment for mild gestational diabetes (MFMU trial) comparing active treatment versus standard obstetric care for mild GDM have been conducted during the years in which the HAPO study was carried out. In both trials, treatment, achieved primarily by diet/lifestyle modification, resulted in reduced risks of fetal overgrowth, shoulder dystocia, cesarean delivery, and hypertensive disorders (3,4). Recruitment processes and glycemic values of participants were not identical in the mentioned two randomized controlled trials and the HAPO observational study. However, there was substantial overlap between glucose values used for inclusion in the randomized controlled trials and those recommended in IADPSG report as new threshold values. Furthermore, frequencies of outcomes such as LGA or birth weight >90th percentile and preeclampsia in usual care versus treatment arms of the randomized controlled trials are similar to those observed in the HAPO study among women with one or more glucose values that meet or exceed the threshold, compared with those with all values below threshold. Although not directly comparable, it was concluded that results of the two randomized controlled trials and HAPO are highly complementary (1).

Conclusion

Current evidence supports direct causal role between maternal glycaemia and fetal/offspring and maternal adverse outcomes. Glucose testing early in pregnancy to detect overt diabetes and again with a 75-g OGTT at 24–28 weeks' of gestation in all pregnancies not already diagnosed with overt diabetes or GDM by early testing represents fundamental changes in strategies for detection and diagnosis of hyperglycemia in pregnancy. Detection and diagnosis of hyperglycemic disorders in pregnancy based on IADPSG criteria will substantially increase the frequency of hyperglycemic disorders in pregnancy. If results indicate overt diabetes treatment and follow-up as for pre-existing diabetes should be started. If results are diagnostic for GDM the pregnant women should be follow-up closely during pregnancy.

References

1. *Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, et al. International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Diabetes Care. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010; 33: 676–82.*
2. *Ali S, Dornhorst A. Diabetes in pregnancy: health risks and management. Postgrad Med J 2011; 87:417–27.*
3. *Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med. 2009 ; 361: 1339–48.*
4. *Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005; 352: 2477–86.*
5. *Evers IM, de Valk HW, Visser GH. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. BMJ. 2004;328(7445):915.*
6. *HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358:1991-2002.*
7. *Blumer I, Hadar E, Hadden DR, Jovanovič L, Mestman JH, Murad MH, et al. Diabetes and pregnancy: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2013;98:4227-49.*
8. *American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014; 37 Suppl 1:S81-90.*
9. *Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Diabetes and pregnancy. Can J Diabetes 2013;37 Suppl 1:S168-83.*
10. *WHO: Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy. Available at: http://www.who.int/diabetes/publications/Hyperglycaemia_In_Pregnancy/en/, Accessed on 28th August 2014.*