Literature Review

Hyperglycemia in Pregnancy: Recent Diagnostic Criteria and Pharmacologic Treatment for Glycemic Control

Hiperglikemi pada Kehamilan: Kriteria Diagnosis Terbaru dan Pengobatan Farmokologik untuk Mencapai Kendali Glikemi

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Abstract

Hyperglycemia in pregnancy, or formerly known as gestational diabetes mellitus, is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. The classical screening and diagnosis of hyperglycemia in pregnancy is the two-steps screening, consists of 50 gram glucose load and follow by 3-hour 100 gram oral glucose test for those who were screening positive. The diagnosis of hyperglycemia in pregnancy is made if at least two abnormal elevated values i.e. fasting > 95 mg/dl, 1 hour > 180 mg/dl. 2 hour > 155 mg/dl, and 3 hour > 140 mg/dl.

The International Association of Diabetes and Pregnancy Study Groups Consensus Panel (IADPSG) in 2010 and the American Diabetes Association in 2011 change the method of screening and diagnostic criteria. In the new method of screening all pregnant woman, not only the high risk group, should be screened using oral glucose tolerance test with 75 gram of glucose. The new diagnosis criteria need only one abnormal plasma glucose value i.e. fasting > 92 mg/dl or 1 hour > 180 mg/dl, or 2 hour > 153 mg/dl. There is debate which criteria should be used universally, since the new criteria will increase the prevalence of hyperglycemia in pregnancy.

In most diabetic clinics, especially in the North America, besides medical nutrition therapy, insulin remains the mainstay of treatment for this patient. However, for those women who cannot afford insulin or do not wish to take insulin, glibenclamide and metformin, may be offered as an alternative. Most experts will prefer to use metformin, since it does not increase body weight and also has an insulin sensitivity effect.

[Indones J Obstet Gynecol 2012; 36-4: 211-6]

Keywords: hyperglycemia in pregnancy, IADPSG criteria, pharmacologic treatment

Abstrak

Hiperglikemi pada saat hamil, atau sebelumnya dikenal dengan nama diabetes mellitus gestasional, didefinisikan sebagai intoleransi karbohidrat yang pertama kali terjadi atau diketahui pada saat hamil. Cara skrining yang lama dikenal dengan skrining dua tahap, terdiri atas tes tantangan glukosa dengan beban glukosa 50 gram dan dilanjutkan dengan tes toleransi glukosa oral beban glukosa 100 gram bagi mereka yang tes tantangan glukosa positif. Diagnosis hiperglikemi saat hamil ditegakkan apabila sedikitnya ditemukan dua angka abnormal dari hasil tes toleranssi glukosa oral yaitu puasa > 95 mg/dl, 1 jam > 180 mg/dl. 2 jam > 155 mg/dl, dan 3 jam > 140 mg/dl.

Pada tahun 2010 The International Association of Diabetes and Pregnancy Study Groups Consensus Panel (IADPSG) dan American Diabetes Association pada tahun 2011 mengubah cara skrining dan kriteria diagnosis yang lama. Cara skrining yang baru mencakup semua wanita hamil, tanpa memperhatikan adanya faktor risiko. Skrining dilakukan dengan tes toleransi glukosa oral beban glukosa 75 gram. Kriteria yang baru hanya membutuhkan satu angka abnormal dari ketiga hasil tes toleransi glukosa oral yaitu puasa > 92 mg/dl, 1 jam > 180 mg/dl, dan 2 jam > 153 mg/dl. Sampai saat ini masih ada ketidaksepakatan kriteria mana yang seharusnya digunakan, mengingat kriteria baru akan meningkatkan prevalensi penderita hiperglikemi saat hamil. Sebagian besar klinik diabetes, khususnya di Amerika Utara, terapi nutrisi medik dan insulin masih merupakan pilihan pengobatan yang digunakan. Apabila penderita tidak dapat menggunakan insulin atau tidak mau suntikan insulin, obat antidiabetik oral seperti glibenklamid dan metformin merupakan terapi alternatif. Kebanyakan ahli memilih menggunakan metformin, oleh karena selain tidak meningkatkan berat badan juga mempunyai efek memperbaiki sensitivitas insulin di jaringan.

[Maj Obstet Ginekol Indones 2012; 36-4: 211-6]

***Kata kunci**: hiperglikemi pada kehamilan, kriteria IADPSG, terapi farmakologik*

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DEFINITION AND PREVALENCE

Gestational diabetes mellitus is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. This definition is applicable regardless of whether insulin is used to treat the disease or even if the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated the pregnancy.[1] This definition is a misnomer, since it includes unrecognized overt diabetes mellitus that may have existed be-

fore pregnancy and hyperglycemia that is diagnosed concurrently with pregnancy. Because the term of gestational diabetes mellitus is confusing, the International Association of Diabetes and Pregnancy Study Groups Consensus Panel (IADPSG) used the term of "hyperglycemia in pregnancy".[2] In this paper we used the term hyperglycemia in pregnancy instead of gestational diabetes mellitus.

The prevalence of hyperglycemia in pregnancy varies due to several factors i.e. the criteria used for the screening, the pregnant women itself either all pregnant women or only the high risk group, the different of ethnic groups. In the last two decades diabetes mellitus is increased all over the world especially among the developing countries. One of the important reason is the increasing of obesity due to changes of lifestyles. Since the prevalence of type 2 diabetes mellitus is increasing, which is mostly cause by insulin resistance, the condition of hyperglycemia in pregnancy may also increased. In the 1960s, using the same criteria of diagnosis, the prevalence of hyperglycemia in pregnancy was around 1- 4%, the current estimates is between 7 - 14%.[3] In Indonesia 1982 the prevalence of diabetes mellitus in Indonesia was only 1.5%,[4-6] while in the year 2000s it is increasing to 9-12%.[7,8] Our own study in Makassar in 1989, the prevalence of gestational diabetes mellitus varies between 2.3%.[9] With the increasing of type 2 diabetes mellitus and obesity in Indonesia in the recent year, especially in women of child bearing age, the prevalence of hyperglycemia in pregnancy will also increased.

SCREENING AND DIAGNOSIS

For many years, the American Diabetes Association (ADA) as well as other countries used a two-step screening and diagnosis of hyperglycemia in pregnancy. This method of screening and diagnosis of gestational diabetes mellitus was the gold standard in the United States.[10] The two-step screening approach consist of first step, the initial screening by measuring the plasma glucose 1- hour after a 50 gram glucose load. The test is positive when the plasma glucose level > 140 mg/dl. Those with positive test will be followed by the second step, the 3 - hour 100 gram oral glucose tolerance test. Gestational diabetes mellitus (the old terminology) was diagnosed if at least two of the four values equal or exceed the cut points of fasting plasma glucose > 95 mg/dl, 1-hour after 100 g glucose of 180 mg/dl, 2-hour of 155 mg/dl, and 3-hour of 140 mg/dl (Figure 1).

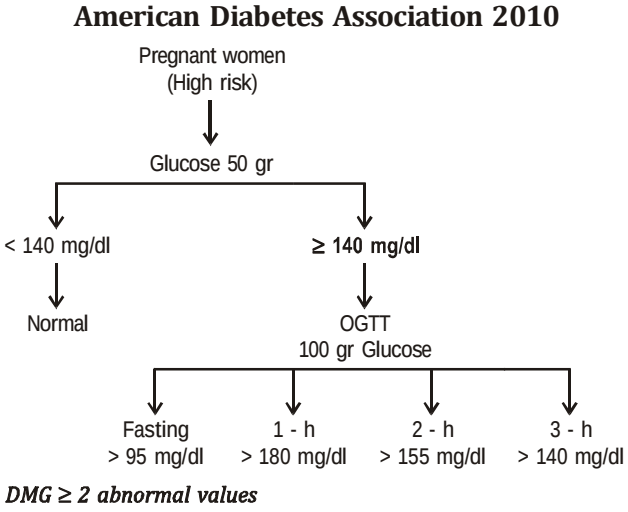

Figure 1. The two step screening and diagnosis of hyperglycemia in pregnancy.

Due to the increasing prevalence of obesity among child bearing age women, the number of women with hyperglycemia in pregnancy will also increase, which carries risks for the mother and also the fetus. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, a multinational epidemiologic study consist of more than 25,000 pregnant women, proved that risk of complication among the mother, fetal, and neonatal continuously increased as an increasing maternal glycemia at 24-28 gestational weeks, even within ranges of previously considered as a normal glycemic range for pregnant women.[11] The results of HAPO study, led to careful reconsideration of the old diagnosis criteria of hyperglycemia in pregnancy. The conclusion of the HAPO study, gave a new cutoffs point for a new criteria of diagnosis hyperglycemia in pregnancy, the fasting plasma glucose ≥ 92 mg/dl, 1-h ≥ 180 mg/dl, and 2-h ≥ 153 mg/dl. The IADPSG in March 2010[2] and ADA in 2011,[12] recommend as follow a) all women not known have prior diabetes mellitus, should undergo a 75 gram OGTT at 24-28 weeks of gestation, b) the diagnosis criteria of hyperglycemia in pregnancy follow the result of the HAPO study i.e fasting plasma glucose > 92 mg/dl, 1-h > 180 mg/dl, and 2-hour > 153 mg/dl (Table 1). Table 1 shows the difference between the old and the new criteria for the diagnosis of hyperglycemia in pregnancy.

Table 1. The old and the new criteria for the diagnosis of hyperglycemia in pregnancy

	Old method	New method
24-28 weeks	Screen high-risk all women gestation	Universal testing of all pregnant women
Screen	1-h 50-g glucose load, nonfasting, glucose loading test; if ≥ 130 or 140, proceed to diagnostic test	None
Diagnostic test	After 8- to 12-h fast, obtain fasting provide 100-g glucose load; then obtain 1-, 2-, and 3-h venous BG	After 8- to 12-h fast, obtain fasting, provide 75-g glucose load, then obtain 1-, and 2-h venous BG
Diagnostic of GDM	If two of the following values meet or exceed: fasting 95 mg/dl, 1-h 180 mg/dl, 2-h 155 mg/dl, 3-h 140 mg/dl	If any 1 values meets or exceeds: fasting 92 mg/dl, 1-h 180 mg/dl 2-h 153 mg/dl

Data from American Diabetes Association. Standards of medical care in diabetes 2011. Diabetes Care 2011; 34 (suppl 1): S11-S61.

This new criteria, the IADPSG criteria, will significantly increase the prevalence of hyperglycemia in pregnancy, primarily because only one abnormal value is needed for the diagnosis. Agarwal et al13 in their study of 10.283 pregnant women undergoing a 75-gram glucose OGTT reported that using the IADPSG will increase the prevalence of hyperglycemia in pregnancy nearly three fold compared to the old ADA criteria.

Treatment goals and methods of treatment

Maternal hyperglycemia with resultant of fetal hyperinsulinemia is central to the pathophysiology of all diabetic complications during pregnancy and delivery. The infants of mother with hyperglycemia in pregnancy are at 3 to 8 fold increased risk stillbirth and macrosomia, spontaneous abortion, congenital anomalies, metabolic complications (hypoglycemia and hypocalcemia), haematologic complications (hyperbilirubinemia and polycytemia), and shoulder dystocia after delivery. These side effects may occur even in a mild hyperglycemia during pregnancy. The Australian Carbohydrate Study in Pregnant Women (ACHOIS) trial, proved that treatment of hyperglycemia in pregnancy reduces serious perinatal morbidity.[14]

Good glycemic control may achieve by exercise and medical nutrition therapy, plus pharmacologic therapy if fail by medical nutrition therapy. Although normoglycemia is the accepted goals of treatment in hyperglycemia in pregnancy, the target goals of blood sugar is still controversies. The ADA suggest the treatment goals is to maintain normoglycemia i.e fasting plasma glucose < 95 mg/dl, 1-h postprandial plasma glucose ≤ 140 mg/dl, and 2-h postprandial ≤ 120 mg/dl.[15] The National Institute for Health and Clinical Excellence (NICE) recommendation for self testing of blood sugar in pregnancy is fasting 63 - 106 mg/dl and 1-hour after postprandial should be < 140 mg/dl.[16] Another guideline, the Canadian Diabetes Association recommends fasting plasma glucose 3.5 to 5.2 mmol/l, 1 hour postprandial 5.5 - 7.7 mmol/l, and 2 hour postprandial 5.0 - 6.6 mmol/l. In our clinic, we use the ADA criteria and all patient with hyperglycemia in pregnancy are advised to have a reflectance meter for self-monitoring of capillary blood sugar at home.

Most patient with hyperglycemia in pregnancy will reach the normoglycemia levels only by lifestyle modification, the medical nutrition therapy and exercise. In our clinic only 15% of them need pharmacologic therapy with insulin.

Insulin

After fails to medical nutrition therapy, around 80-90% of hyperglycemia in pregnancy need insulin therapy. Since the use of insulin in 1922, the perinatal mortality rate decreased near to non-diabetic pregnancy (Figure 2).[17] At the moment we have two kinds of insulin, the human insulin and the analogues insulin. Human insulin has been used for years, and it is safe since it does not transfer to placenta. The analogues insulin has several benefits compared to human insulin such as greater convenience in he timing of injection (just before meals while human insulin should be 30 minutes before meals), less hypoglycemia effects. Until now, there are only three analogues insulin agreed to use in pregnancy, insulin lispro (Humulin), insulin aspart (Novorapid) and glargin (Lantus).[18-20]

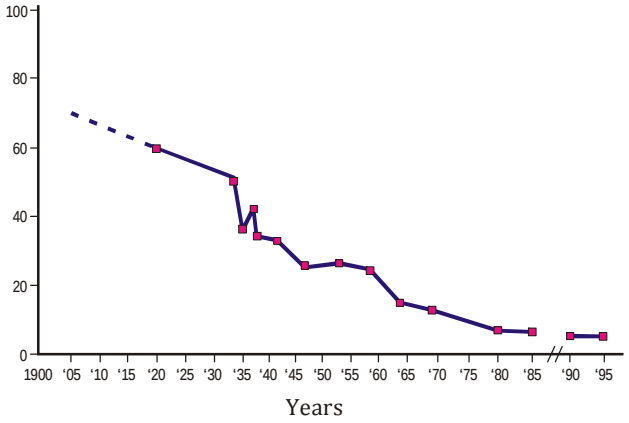

Figure 2. The reduction of perinatal mortality after the era of insulin.[17]

The dose of insulin depends of the bodyweight of the patient before pregnancy. In non-obese patients insulin dose is 0,8 U/kg, but for obese subjects insulin requirement is 0,9 U/kg. The administration of insulin depends on the fluctuation of blood sugar. For many patients with hyperglycemia in pregnancy, increase of fasting plasma glucose is the only abnormal glucose value. In such patients, a single morning injection of 10 U long-acting insulin such NPH insulin is sufficient to achieve euglycemia throughout 24 hour. For some patients may need more than one injection such as fixed-dose combination of 70% intermediate acting insulin and 30% of short acting insulin.[15] It is advised to reach this strict target goals, self-monitoring of blood glucose before every insulin injection is recommended.

Oral Hypoglycemic Agents

The use of oral hypoglycemic agents in patients with hyperglycemia in pregnancy has been one of the biggest controversies in the treatment of diabetes and pregnancy. A variety of oral hypoglycemic agents is now available for lowering blood glucose. For patients with pregnancy and hyperglycemia, the most important is that the agent should not cross the placenta from the maternal to fetal circulation in significant amounts. Because most patients with hyperglycemia in pregnancy were identified between 24 - 28 of gestation, the fetus is not exposed to the drug during the period of organogenesis.

The first report using oral hypoglycemic agents in patients with diabetes and pregnancy was reported by Coetzee et al from Cape Town South Africa in 1974.[21] In their study, metformin and glybenclamide were used. Metformin was used for obese patients and glibenclamide for normoweight. From their study, the conclusion was using oral hypoglycemic agent, either metformin or glibenclamid was better compared to those only in dietary treatment or without treatment. In their study the conclusion was "*we believe that the secret of successful perinatal outcomes in all pregnant diabetic patients lies more in the achievement of excellent blood glucose levels than in the means of achieving it*". For several years, around 25 years, there was no publication about oral hypoglycemic agents in diabetes and pregnancy.

Glibenclamide

Glibenclamide or glyburide in USA, was used for the treatment for hyperglycemia in pregnancy since it is less crossing the placenta (only 3.9%) compared to the other sulfonylurea agents. Langer et al[22] in 2000 for the first time reported their study to compare glybenclamide and insulin in patients with hyperglycemia in pregnancy. The authors compared glybenclamide and standard insulin therapy in randomized control trial of 404 patients. The target goals for glucose was fasting 60-90 mg/dl, prepradial 80-95 mg/dl, and 2-h postprandial < 120 mg/dl. The results of their study was the perinatal morbidity such as incidence of macrosomia, neonatal metabolic complications (hypoglycemia, polycythemia, hyperbilirubinemia) respiratory distress and cesarian delivery, are comparable between the two groups. If the patient fail to reach the target goals than they have to be switched to insulin therapy. The failure rates with glybenclamide was reported between 16 to 21%, mostly due to poor glycemi control and some by hypoglycemia effect in the mother.

Metformin

Different than glibenclamide, metformin can reduce the blood sugar by reducing hepatic glucose output from the liver, increasing peripheral glucose uptake by the liver, muscle and adipose tissues. The actions of this agent does not cause insulin secretion hence does not cause hypoglycemic effect. Rowan and his colleagues[23] (MiG Trial Investiga-

tion) in 2008 published their study on metformin in hyperglycemia in pregnancy. In this study 751 patients were randomized to two different treatment either metformin or insulin. The rate of primary composite outcome of neonatal morbidity, included neonatal hypoglycemia, respiratory distress, prematurity, and birth trauma was not significant different between the two groups, for the metformin group was 32.0% and insulin group 32.2%. One important results which is different between the two groups was severe hypoglycemia in the neonatal, only 3.3% among the metformin treatment and 8.1% in the insulin therapy.

The Controversies of Treatment

Even if the patient with hyperglycemia in pregnancy does not have high abnormal glucose intolerance, all experts agree that treatment either by lifestyle modification only, or lifestyle modification plus pharmacologic treatment is always needed to reach the excellent target goals. For years insulin was the only treatment of choice for this patient. The choice of insulin is still controversy, especially the used of insulin analogue. This kind of insulin used in pregnant diabetic patients just started 10 years ago. The human insulin is preferable since it has been used for years without side effect in the neonates or even long-term effect among the children.

The use of oral agents, metformin and glibenclymide, is still the biggest controversy in diabetology. American Diabetes Association in the recent Clinical Practice Recommendation 2012,[24] the diagnosis of women with hyperglycemia follow the new criteria but there was no statement about the treatment, which means that insulin is still the only pharmacologic therapy. In 2009 the International Diabetes Federation of World Health Organization statement as follow "for women with GDM who exceed predetermined glycemic goals, insulin is the preferred treatment. Where insulin cannot be afforded, or where circumstances make its use hazardous, then oral agents can be the only option". In our clinic, insulin is still the only choice for the treatment diabetic patients complicated with hyperglycemia.

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