PERINATAL JOURNAL

Review

Perinatal Journal 2014;22(1):42-52

Screening and diagnostic tests in gestational diabetes: state of the art

Selahattin Kumru[1,2]

[1]*Department of Obstetrics and Gynecology, Faculty of Medicine, Düzce University, Düzce, Turkey*
[2]*Antalya Training and Research Hospital of Health Ministry, Antalya, Turkey*

Abstract

Gestational diabetes mellitus (GDM) is defined as diabetes mellitus (DM) seen during pregnancy. It has been long known that pregnant women diagnosed with gestational diabetes mellitus have more maternal and perinatal risks than healthy pregnant women, and it is noted that the increase of such risk can be prevented by GDM screening-diagnosis, and the treatment of cases diagnosed. There are many screening and diagnostics tests for gestational diabetes mellitus; however, there is no consensus on a particular test for best screening. It has been in search of new test methods after the data of Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study of which data have been published recently where it was emphasized that the values accepted as "normal" in the current tests also increase maternal and perinatal risk. As a result, a study group called IADPSG (International Association of the Diabetes and Pregnancy Study Group) studied the recommendations of HAPO study, and has recommended 75-g diagnostic test with new threshold values instead of current GDM screening / diagnostic tests. Today, it has been discussed what advantages and disadvantages are included in terms of efficiency, cost and benefit if the advices of IADPSG are followed for universal screening. This review has been prepared to present up-to-date information about these discussions and current status

Key words: Gestational diabetes mellitus, screening.

Gebelik diyabetinde tarama ve tanı testleri: Güncel durum

Gestasyonel diabetes mellitus (GDM), gebelikte ortaya çıkan DM olarak tanımlanmaktadır. Gestasyonel diabetes mellitus tanısı alan gebelerin, sağlıklı gebelerden daha fazla maternal ve perinatal risk taşıdığı öteden beri bilinmekte, GDM tarama-tanısı, tanı alan olguların tedavisi ile de bu risk artışının engellenebileceği ifade edilmektedir. Gestasyonel diabetes mellitus için pek çok tarama ve tanı testi mevcut olup hangi testin tarama için uygun olduğu konusunda fikir birliği mevcut değildir. Son zamanlarda verileri yayımlanan HAPO *(Hyperglycemia and Adverse Pregnancy Outcome)* çalışması, mevcut testlerde ''normal'' olarak kabul edilen değerlerin de maternal ve perinatal risk artışı ile birlikte olduğunu vurgulamasından sonra yeni arayışlar başlamıştır. Yeni arayışlar neticesinde IADPSG *(International Association of the Diabetes and Pregnancy Study Group)* adında bir çalışma grubu HAPO çalışmasının önerileri üzerinde çalışmış, mevcut GDM tarama/tanı testlerinin yerine yeni eşik değerleri ile 75 g tanı testini önermiştir. Bugün için IADPSG önerilerinin universal tarama için kullanımı durumunda etkinlik, maliyet, fayda yönünden ne tür avantaj ve dezavantajlar içerdiği tartışılmaktadır. Eldeki derleme bu tartışmalar ve güncel durum ile ilgili güncel bilgileri aktarmak amacıyla hazırlanmıştır.

Anahtar sözcükler: Gestasyonel diabetes mellitus, tarama.

Introduction

Gestational diabetes mellitus (GDM) is defined as the glucose intolerance starting with pregnancy or diagnosed in pregnancy for the first time.[1] Insulin resistance and diabetic susceptibility appear due to hormonal changes during pregnancy.[2] Diabetes during pregnancy is accompanied by the increase in maternal and perinatal morbidity. Some of them are preeclampsia, preterm labor, cesarean delivery, neonatal hyperbilirubinemia, shoulder dystocia, and birth trauma.[3]

Up-to-date data report that many gestational complications may be decreased and perinatal outcomes may be improved by means of GDM screening and treatment.[4-6]

Correspondence: Dr. Selahattin Kumru, MD. Düzce Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı, Düzce, Turkey.
e-mail: selahattinkumru@gmail.com

Received: October 21, 2013; **Accepted:** January 29, 2014

Available online at:
www.perinataljournal.com/20140221012
doi:10.2399/prn.14.0221012
QR (Quick Response) Code:

Table 1. The comparison of tests and threshold values used for gestational diabetes mellitus.

Approach	Glucose amount (gram)	Diagnosis criteria	Glucose threshold, mmol/L (mg/dl)				Abnormal value (n)
			Fasting	1-hour	2-hour	3-hour	
2-step	100	NDDG	5.8 (105)	10.5 (190)	9.1 (165)	8.0 (145)	2
2-step	100	CC	5.3 (95)	10.0 (180)	8.6 (155)	7.8 (140)	2
2-step	75	ADA (2000-2010)	5.3 (95)	10.0 (180)	8.6 (155)	-	2
2-step	75	CDA (2008)	5.3 (95)	10.6 (191)	8.9 (160)	-	2
1-step	75	IADPSG	5.1 (92)	10.0 (180)	8.5 (153)	-	1
1-step	75	WHO	6.1 (110)	-	7.8 (140)	-	1

ADA: American Diabetes Association; **CC:** Carpenter-Coustan; **CDA:** Canadian Diabetes Association; **IADPSG:** International Association of the Diabetes and Pregnacy Study Groups; **NDDG:** National Diabetes Data Group; **WHO:** Wold Health Organization. Adapted from NIH.[7]

Screening Tests used for Gestational DM

Screening tests are the tests conducted in order to identify diseases considered as a frequent and significant health issue in a society and to reveal the group to be applied diagnostic test. For performing screening test, there are some prerequisites such that the screened disease should be a significant disease in that society, there should be an active "diagnostic test" for a group which is found to be positive in screening, and screening test should be easily applicable, acceptable by society and cost-effective. In addition, there should be an efficient "treatment" method for cases diagnosed with "diagnostic test" applied those who are found to be "positive" in screening test. One of the most significant tests expressing the importance of screening tests is cervical smear practices used for screening cervical pre-invasive lesions. By means of the treatment of smear screenings and pre-invasive lesions, cervical invasive cancer incidence decreases day by day.

There are some problems with the tests suggested and applied for the screening of gestational diabetes mellitus. First of all, there are many screening tests. Almost all of these tests have different cut-off values. Additionally, some organizations (i.e. WHO – World Health Organization) suggests one-step diagnostic test instead of screening test. Due to all these reasons, there is no consensus today on the best test for GDM screening and diagnosis.[7] As seen in the **Table 1**, there are many screening/diagnostic tests for GDM, different values are suggested and used as both screening positivity and diagnostic criteria. Some associations recommend to apply diagnostic test to those who are found to be positive in the screening test while International Association of the Diabetes and Pregnancy Study Group (IADPSG) and WHO recommend single-step diagnostic test.

There are differences in the sensitivity and specificity values in the assessment, in terms of the efficiency, of the tests recommended for screening and diagnosis of gestational diabetes mellitus and sensitivity and specificity values vary according to threshold values used (**Table 2**).[7]

HAPO Study

Presence of many screening and diagnostic tests and the threshold values used in these tests being different show that additional studies are needed to help for clarifying the situation about the hyperglycemia in pregnancy. Therefore, in order to clarify the current situation, Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study was planned. The study was designed as an observational study and conducted in 9 countries simultaneously. The data of 23,316 out of 25,505 pregnant women, who were applied 75-g OGTT (oral glucose-tolerance test), were analyzed and the results were published in 2008.[8]

The pregnant women in HAPO study were categorized into 7 groups according to fasting, postprandial 1-hour and 2-hour plasma glucose levels where fasting plasma glucose (FPG) was considered as <75-<100 mg/dl, 1-hour plasma glucose level (1hPG) as <105-<212 mg/dl, and postprandial second hour value as <90-178 mg/dl. Perinatal outcomes were evaluated in the 7 group, and C-peptide levels were measured in newborn cord blood. The data of the study revealed that the rate of birth weight being higher than 90th percentile increases, the rate of primary cesarean delivery increases, the rate of clinical neonatal hypoglycemia increases, and the rate of C-peptide level in cord blood being higher than 90th percentile increases as the plaFPG, 1hPG and 2hPG levels (**Fig. 1**).

Table 2. Various GDM screening tests and efficiencies.

Threshold value	Studies (n)	Screening test	Criteria	Sensitivity (95% CI, %)	Specificity (95% CI, %)	LR+ (95% CI)	LR- (95% CI)
≥7.8 mmol/L (≥140 mg/dl)	9	50-g OGCT	CC	85 (76-90)	86 (80-90)	5.9 (4.2-8.3)	0.18 (0.11-0.29)
≥7.8 mmol/L (≥140 mg/dl)	3	50-g OGCT	ADA (2000-2010)	86 (86-97)	84 (79-87)	6.0 (5.1-7.0)	0.16 (0.06-0.45)
≥7.8 mmol/L (≥140 mg/dl)	7	50-g OGCT	NDDG	85 (73-92)	83 (78-87)	5.1 (3.9-6.6)	0.18 (0.10-0.34)
≥7.8 mmol/L (≥140 mg/dl)	1	50-g OGCT	CDA	81 (58-95)	69 (59-79)	2.6 (1.8-3.8)	0.27 (0.11-0.67)
≥7.8 mmol/L (≥140 mg/dl)	3	50-g OGCT	WHO	70 (43-85)	89 (73-94)	6.5 (5.1-8.3)	0.33 (0.22-0.52)
≥7.2 mmol/L (≥130 mg/dl)	6	50-g OGCT	CC	99 (95-100)	77 (68-83)	4.2 (3.0-5.9)	0.02 (0.003-0.08)
≥7.2 mmol/L (≥130 mg/dl)	3	50-g OGCT	NDDG	88 (67-90)	66 (47-84)	2.7 (1.8-3.9)	0.14 (0.34-0.55)
≥12.2 mmol/L (≥220 mg/dl)	1	50-g OGCT	CC	17 (12-24)	100 (99-100)	Undefined	0.83 (0.78-0.89)
≥4.7 mmol/L (≥85 mg/dl)	4	FPG	CC	87 (81-91)	52 (50-55)	1.8 (1.6-2.0)	0.25 (0.16-0.38)
≥5.0 mmol/L (≥90 mg/dl)	4	FPG	CC	77 (66-85)	76 (75-77)	3.2 (2.9-3.6)	0.30 (0.20-0.46)
≥5.1 mmol/L (≥92 mg/dl)	3	FPG	CC	76 (26-80)	92 (90-95)	7.4 (4.0-13.9)	0.27 (0.13-0.54)
≥5.3 mmol/L (≥95 mg/dl)	5	FPG	CC	54 (32-74)	93 (90-96)	8.2 (5.9-11.5)	0.49 (0.31-0.79)
%5.0	1	HbA1c	CC	92 (86-96)	28 (23-33)	1.3 (1.2-1.4)	0.28 (0.15-0.50)
%5.3	1	HbA1c	IADPSG	12 (7-18)	97 (95-98)	3.9 (2.0-7.7)	0.91 (0.86-0.97)
%5.5	1	HbA1c	ADA (2000-2010)	86 (72-95)	61 (57-65)	2.2 (1.9-2.6)	0.23 (0.11-0.48)
%7.5	1	HbA1c	ADA (2000-2010)	82 (72-90)	21 (17-26)	1.0 (0.93-1.2)	0.85 (0.52-1.4)

ADA: American Diabetes Association; **CC:** Carpenter-Coustan; **CDA:** Canadian Diabetes Association; **FPG:** fasting plasma glucose; **HbA1c:** Hemoglobin A1C; **IADPSG:** International Association of the Diabetes and Pregnacy Study Groups; **LR+:** positive likelihood ratio; **LR-:** negative likelihood ratio; **NDDG:** National Diabetes Data Group; **OGCT:** oral glucose challenge test; **WHO:** Wold Health Organization. Adapted from Donovan et al.[7]

The authors expressed that when they performed additional analyses in order to find out whether FPG, 1hPG and 2hPG values were correlated better with poor perinatal outcome, they found that both FPG, 1hPG and 2hPG values were correlated with poor perinatal outcomes, that neither preprandial nor postprandial values were stronger against each other in this correlation with poor perinatal outcomes, that the risk of poor perinatal outcome increased as both preprandial and postprandial blood glucose levels increase, and that they could not found any "threshold value" to use for the increase of poor outcomes (**Table 3**).

The results of observational study indicated that the risk of poor perinatal outcome increases as both preprandial and postprandial plasma glucose levels increase and no specific threshold value can be calculated for the risk increase while, on the other hand, the risk increase for perinatal morbidity continues in the values considered as "normal" today. Therefore, the authors suggested to change threshold values currently accepted.

IADPSG Recommendations

In accordance with the findings and recommendations of HAPO study explained above, IADPSG was arranged in order to review the findings obtained in HAPO study and to establish a new screening/diagnostic method in accordance with HAPO recommendations. The group considered basal relative risk (RR) as "1" for the risk (complication rate) observed (FPG <95 mg/dl, 1hPG <105 mg/dl and 2hPG <90 mg/dl) according to basal risk and made RR calculation for each category, and by considering "RR >1.75" as a risk increase, the new corresponding values were recommended as new threshold values. As a result of these calculations, for the FPG checked after 8 hours of fasting and postprandial first hour and second hour blood glucose levels checked after 75-g oral glucose loading, it was recommended to define values for FPG above 92 mg/ml, 1hPG above 180 mg/ml, and 2hPG above 153 mg/ml as "high", and to establish GDM diagnosis in the presence of a single high value.[9]

Potential Conditions that May Arise by Practicing IADPSG Recommendations (Cost/Benefit)

Additional benefits to be contributed to the current screening-diagnostic strategies by practicing IADPSG recommendations clinically, complication risks that pregnant women may be exposed who are not diag-

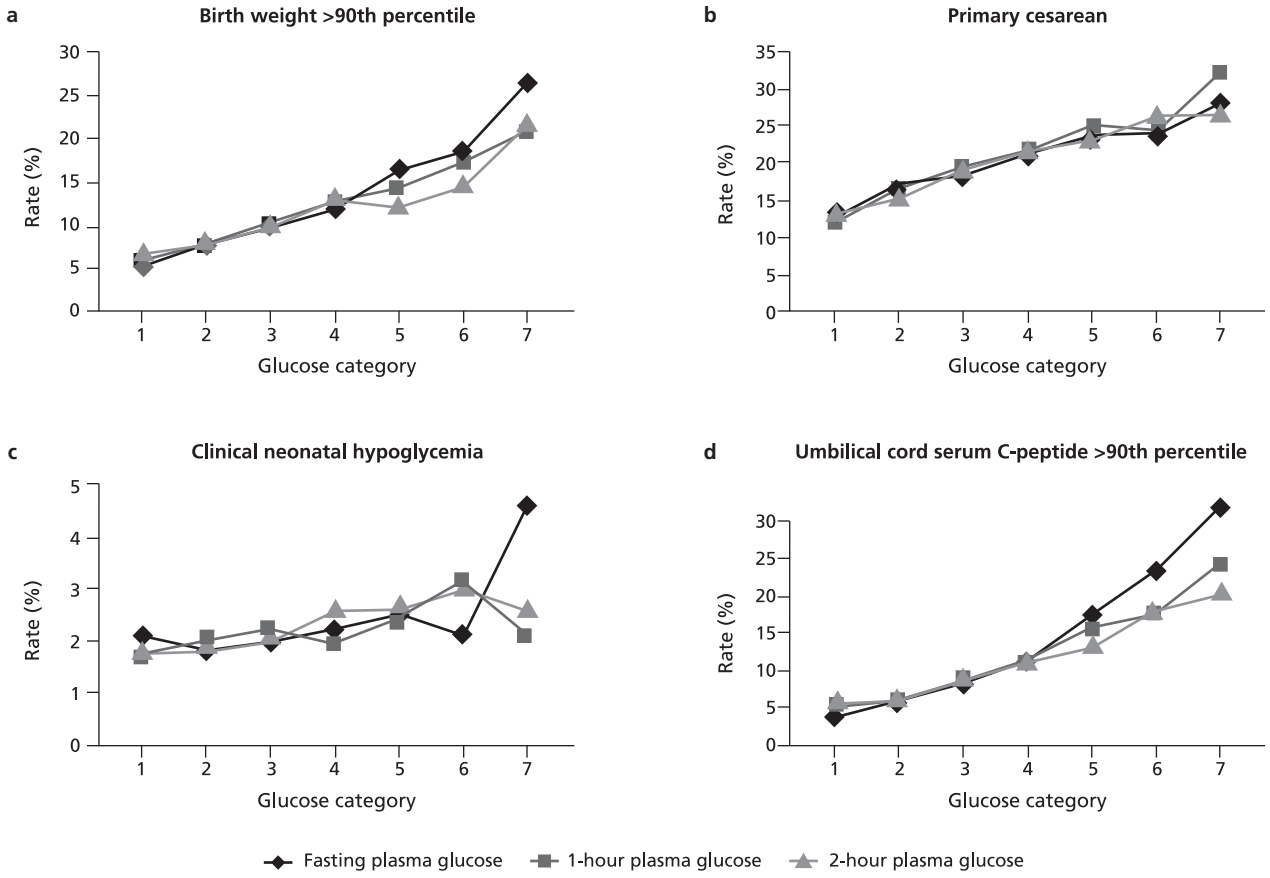

Fig. 1. Primary outcome rates according to glucose categories. The fasting glucose categories are 1: <75 mg/dl, 2: 75-79 mg/dl, 3: 80-84 mg/dl, 4: 85-89 mg/dl, 5: 90-94 mg/dl, 6: 95-99 mg/dl, 7: 100 mg/dl and above, respectively. The 1-hour plasma glucose levels are 1: <105 mg/dl, 2: 106-132 mg/dl, 3: 133-155 mg/dl, 4: 156-171 mg/dl, 5: 172-193 mg/dl, 6: 194-211 mg/dl, 7: 212 mg/dl and above, respectively. The 2-hour plasma glucose levels are 1: <90 mg/dl, 2: 91-108 mg/dl, 3: 109-125 mg/dl, 4: 126-139 mg/dl, 5: 140-157 mg/dl, 6: 158-177 mg/dl, 7: >178 mg/dl, respectively. Adapted from The HAPO Study Cooperative Research Group.[8]

nosed and evaluated as "normal" so no treatment is received in accordance with IADPSG recommendations, and in return, financial burden to be placed by screening and diagnosing according to IADPSG recommendations are among the significant topics which have been still debated.

Bodmer-Roy et al. from Montreal, Canada[10] evaluated retrospectively the results of pregnant women who were not diagnosed as GDM in accordance with the protocol currently followed but should be diagnosed as GDM according to IADPSG criteria, and the results of pregnant women who were not diagnosed as GDM (having normal values) according to their criteria and IADPSG criteria. GDM screening is carried out in accordance with the recommendations of Canada Diabetes Association (CDA) in Canada, and after 50 g glucose loading test, first hour value below 137 mg/dl is considered as normal, first hour value above 184 mg/dl is considered as diabetes, and 75 g is loaded if first hour value is between 137 and 184 mg/dl. The threshold values for 75-g OGTT are considered as 96, 191 and 160 mg/dl for FPG, 1hPG and 2hPG respectively.[10] The perinatal outcomes of the pregnant women who were not diagnosed as GDM in accordance with the protocol currently followed but should be diagnosed as GDM according to IADPSG criteria were analyzed, and the cases with FPG between 92 and 96 mg/dl, 1hPG between 180 and 191 mg/dl and 2hPG between 153 and 160 mg/dl were concluded as the cases between two protocols (**Fig. 2**). The authors determined that there were some differences in terms of demographic characteristics

Table 3. Odds ratio (AOR) values with adjusted primary outcome according to blood glucose categories.

Glucose category	Plasma glucose level					
	Fasting		1-hour		2-hour	
	Total number 95% CI	Odds ratio	Total number 95% CI	Odds ratio	Total number 95% CI	Odds ratio
Birth weight > 90th percentile						
1	4035 (213)	1.00	4177 (268)	1.00	4264 (297)	1.00
2	7501 (572)	1.37 (1.16-1.62)	7524 (584)	1.21 (1.04-1.41)	7422 (587)	1.11 (0.96-1.30)
3	6168 (622)	1.72 (1.46-2.03)	6003 (593)	1.65 (1.41-1.93)	5865 (580)	1.51 (1.30-1.75)
4	2741 (323)	1.95 (1.62-2.35)	2768 (352)	2.27 (1.91-2.71)	3024 (396)	2.15 (1.82-2.54)
5	1883 (310)	2.73 (2.25-3.31)	1858 (264)	2.66 (2.19-3.21)	1720 (210)	2.10 (1.73-2.56)
6	672 (124)	3.00 (2.34-3.86)	645 (111)	3.50 (2.72-4.50)	690 (101)	2.68 (2.08-3.45)
7	217 (57)	5.01 (3.54-7.09	242 (49)	4.49 (3.16-6.39)	232 (50)	4.46 (3.15-6.33)
Primary cesarean						
1	3721 (495)	1.00	3826 (458)	1.00	3903 (535)	1.00
2	6806 (1151)	1.19 (1.06-1.34)	6792 (1113)	1.21 (1.07-1.36)	6664 (1032)	0.97 (0.86-1.09)
3	5483 (1014)	1.21 (1.07-1.37)	5311 (1032)	1.26 (1.11-1.42)	5201 (1017)	1.11 (0.99-1.26)
4	2378 (506)	1.33 (1.15-1.54)	2425 (522)	1.31 (1.13-1.52)	2650 (583)	1.15 (1.00-1.32)
5	1601 (380)	1.44 (1.23-1.69)	1623 (407)	1.48 (1.26-1.74)	1506 (350)	1.17 (0.99-1.37)
6	560 (134)	1.39 (1.11-1.75)	547 (132)	1.30 (1.04-1.64)	615 (162)	1.32 (1.08-1.63)
7	183 (51)	1.60 (1.12-2.27)	208 (67)	1.86 (1.35-2.57)	193 (52)	1.28 (0.91-1.81)
Clinical neonatal hypoglycemia						
1	4043 (83)	1.00	4183 (72)	1.00	4266 (78)	1.00
2	7503 (144)	0.91 (0.69-1.21)	7523 (153)	1.12 (0.84-1.49)	7421 (134)	0.87 (0.66-1.17)
3	6164 (122)	0.92 (0.68-1.23)	6003 (131)	1.24 (0.92-1.68)	5868 (117)	0.96 (0.71-1.30)
4	2744 (59)	1.00 (0.70-1.43)	2772 (54)	1.11 (0.77-1.62)	3027 (80)	1.23 (0.88-1.71)
5	1884 (48)	1.19 (0.81-1.75)	1860 (45)	1.48 (0.99-2.22)	1720 (44)	1.13 (076-1.68)
6	672 (14)	1.01 (0.55-1.84)	643 (20)	2.17 (1.28-3.69)	693 (21)	1.36 (0.81-2.28)
7	217 (10)	1.98 (0.97-4.05)	243 (5)	1.29 (0.51-3.31)	232 (6)	1.12 (0.47-2.67)

Adapted from Donovan et al.[8]

between 186 pregnant women evaluated as "normal" by them who should be diagnosed as GDM according to IADPSG criteria and the pregnant women who were evaluated as normal according to both their criteria and IADPSG criteria (**Table 4**); however, there was no difference among these two groups in terms of perinatal outcomes (**Table 5**). They reported that the gestational outcomes of the pregnant women who were non-diabetic according to CDA but diabetic according to IADPSG were similar, and that more randomized controlled studies are required to put the IADPSG criteria into practice.

Wendland et al. from Brazil[11] carried out and published a meta-analysis in order to compare WHO and IADPSG criteria and perinatal outcomes of the pregnant women who were diagnosed and not treated according to these criteria. In other words, they compared the outcomes of pregnant women who were not treated although they were diagnosed as GDM according to WHO and IADPSG criteria. The results of 44,829 pregnant women were included to the meta-analysis, and they were all the cases who had universal screening procedure. By this study, the authors found that there was perinatal risk increase in the pregnant women who were diagnosed as GDM according to both WHO and IADPSG criteria. They calculated that RRI was 1.53 (95% CI 1.39-1.69; p<0.001) for LGA (large for gestational age), 1.69 (95% CI 1.31-2.18; p<0.001) for preeclampsia, 1.55 (95% CI 0.88-2.73; p=0.13) for perinatal mortality, and 1.37 (95% CI 1.24-1.51; p<0.001) for primary C/S when GDM diagnosis was established according to WHO criteria. The authors reported that the risk for LGA (RR:1.73 95% CI 1.28-2.35, p=0.01), preeclampsia (RR:1.71 95% CI 1.37-2.14, p < 0.001), perinatal mortality (RR:1.40 95% CI 0.91-2.14, p =0.122) and primary C/S (RR:1.23 95% CI 1.01-1.51, p=0.044) increased for the pregnant women who were diagnosed as GDM according to IADPSG criteria, and these risk increases were similar (**Fig. 3**), there was

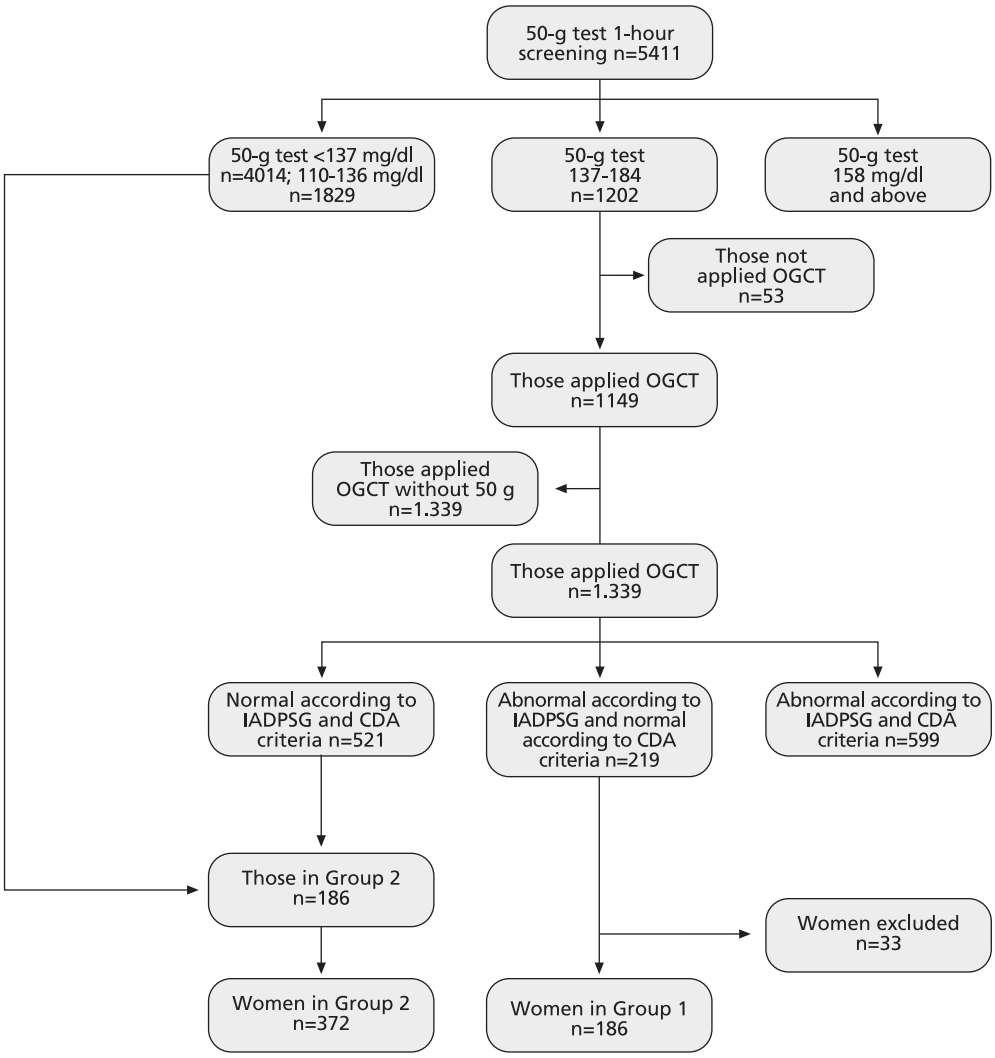

Fig. 2. The formation of groups and selection of samples in Bodymer-Roy et al.'s study. **IADPSG:** International Association of Diabetes and Pregnancy Study Group. **CDA:** Canadian Diabetes Association. Adapted from Bodmer-Roy et al.[10]

compliance among the studies for WHO criteria but there was no compliance among the studies for IADPSG criteria, and additional studies were required to put IADPSG criteria into practice.[11]

In 2013, Falavigna et al.[12] published a simulation study to analyze whether GDM diagnosis and treatment according to WHO and IADPSG criteria decrease perinatal morbidity or not, and if there is a decrease, to find out how many pregnant woman should be screened per case. In the study, GDM prevalence according to WHO and IADPSG criteria and basal GDM prevalence were compared, and then it was looked for an answer for the rates of LGA, preeclampsia and delivery by cesarean in the pregnant women who were and were not treated. Accordingly, it was calculated that GDM prevalence would be approximately 10% according to WHO 1999 criteria, and 15% according to IADPSG criteria (1.5 times more than WHO), and that the risks for LGA, preeclampsia and delivery by cesarean would increase in those who were diagnosed according to both criteria (**Table 6**), and these risk increases could be prevented by treatment.

Table 4. Maternal characteristics in Bodymer-Roy et al.'s study.

	Group 1 n=186	Group 2 n=372	Odds ratio or mean difference (95% CI)	p
Age	31.1±5.6	30.4±5.1	+0.71 (-0.22 to+1.64)	.14
Age>35	51 (27.4)	74 (19.9)	1.52 (1.01-2.29)	.05
Smoking	14 (7.7) (n=182)	29 (7.9) (n=369)	0.98 (0.50-1.90)	>.99
1First trimester weight (kg)	70.12±15.8 (n=181)	65.7±15.4 (n=365)	+4.41 (+1.63 to+7.19)	.002
Weight at the end of pregnancy (kg)	83.8±15.2 (n=177)	79.5±15.5 (n=363)	+4.29 (+1.52 to+7.05)	.002
First trimester BMI (kg/m^2)	26.2±5.4 (n=163)	24.6±5.1 (n=337)	+1.54 (+0.57 to+2.52)	.002
Obesity	36 (20.7) (n=174)	47 (12.9) (n=363)	1.75 (1.09-2.83)	.02
Caucasian	132 (71.0)	257 (69.1)	0.91 (0.62-1.34)	.70
Multipara	107 (57.5)	205 (55.1)	1.10 (0.77-1.57)	.65
Parity (3 and above)	14 (7.5)	14 (3.8)	2.08 (0.97-4.46)	.07
Previous gestational complication*				
GDM	9 (8.4)	6 (2.9)	3.05 (1.06-8.80)	.048
LGA	9 (8.4)	16 (7.8)	1.09 (0.46-2.54)	.83
Intrauterine fetal death	7 (6.5)	9 (4.4)	1.52 (0.55-4.21)	.43
Delivery by cesarean	31 (29.0)	44 (21.5)	1.49 (0.86-2.55)	.16
Chronic maternal conditions†				
Asthma	9 (4.8)	26 (7.0)	0.68 (0.31-1.48)	.36
Chronic hypertension	9 (4.8)	12 (3.2)	1.53 (0.63-3.69)	.35
Thrombotic disease	7 (3.2)	12 (3.8)	1.17 (0.45-3.03)	.81
Hemoglobinopathy	6 (3.2)	16 (4.3)	0.74 (0.29-1.93)	.65
Fibroma	7 (3.8)	8 (2.2)	1.78 (0.64-5.00)	.28

CI: confidence interval; **BMI:** body mas index; **GDM:** gestasyonel diabetes mellitus; **LGA:** large for gestational age. Data given as mean±standard deviation or percentage. *Only multipara women. †One patient may have more than one condition. Adapted from Bodmer-Roy et al.[10]

When the numbers of cases which were needed to be screened to prevent a complication are considered (**Table 7**), the authors reported that the positive contributions of universal GDM screening and treatment to gestational outcomes are "just moderate", that the impact of diagnosis and treatment according to

Table 5. Primary maternal and neonatal complications in Bodymer-Roy et al.'s study.

	Group 1 n=186	Group 2 n=372	Odds ratio or adjusted odds ratio*and mean difference (95% CI)	p
LGA*	17 (9.1)	22 (5.9)	1.58 (0.799-3.13)	.19
Delivery complications	69 (37.1)	112 (30.1)	1.37 (0.95-1.98)	.10
Assisted vaginal delivery	17 (9.1)	34 (9.1)	1.00 (0.54-1.84)	>.99
Delivery by cesarean	31 (16.7)	45 (12.1)	1.45 (0.89-2.39)	.87
Shoulder dystocia	2 (1.1)	6 (1.6)	0.66 (0.13-3.32)	.73
Bleeding during delivery	22 (11.8)	31 (8.3)	1.48 (0.83-2.63)	.22
Major laceration	23 (19.5)	38 (13.7)	1.53 (0.87-2.70)	.17
Preeclampsia*	12 (6.5)	10 (2.7)	2.40 (0.92-6.27)	.07
Prematurity	12 (6.5)	22 (5.9)	1.10 (0.53-2.27)	.85
Neonatal complication at birth	25 (13.4)	36 (9.7)	1.45 (0.84-2.49)	.20
Apgar <7	5 (2.7)	5 (1.3)	2.03 (0.58-7.09)	.31
pH <7.2	21 (12.1) (n=174)	33 (9.5) (n=346)	1.30 (0.73-2.33)	.37
Oxygen support for more than 12 hours	4 (2.2)	6 (1.6)	1.34 (0.37-4.81)	.74
Neonatal complications	20 (10.8)	53 (14.2)	0.73 (0.42-1.26)	.29
Hypoglycemia	4 (2.2)	16 (4.3)	0.49 (0.16-1.48)	.24
Phototherapy	14 (7.5)	26 (7.0)	1.08 (0.55-2.13)	.86
Neonatal hemoglobin >20 g/dl	4 (2.2)	21 (5.6)	0.37 (0.12-1.09)	.08

CI: confidence interval; **LGA:** large for gestational age. Data are given as n (%). *Preeclampsia and LGA rates are adjusted according to effective factors. Adapted from Bodmer-Roy et al.[10]

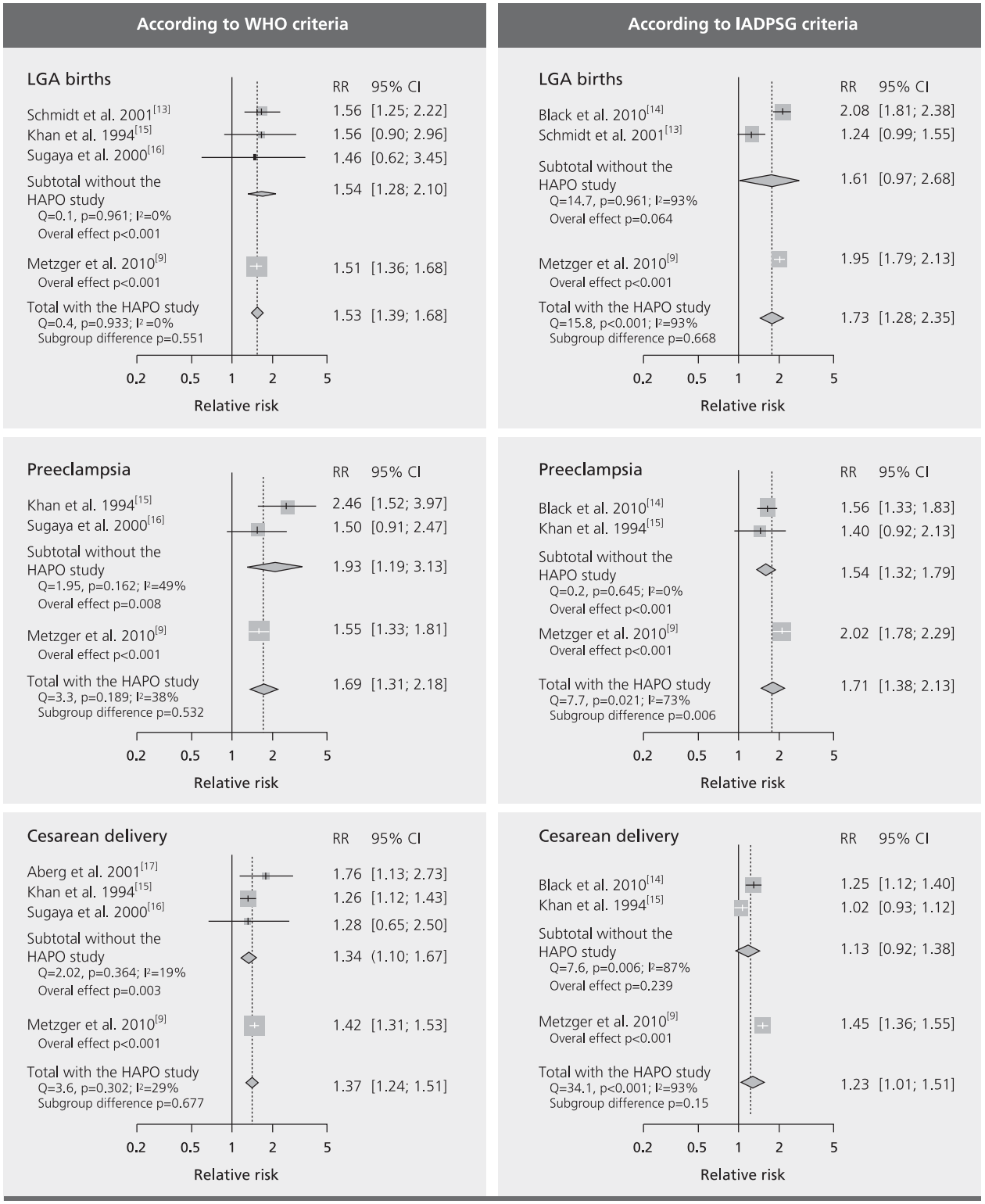

Fig. 3. Sensitivity analysis except HAPO study. **HAPO:** Hyperglycemia and Adverse Pregnancy Outcome; **LGA:** large for gestational age; **RR:** relative risk. Adapted from Wendland et al.[11]

Table 6. Parameters used in the model of Falavigna et al.'s study.

Parameter	Basal value	Lower limit
GDM prevalence according to 1999 WHO criteria	10%	-
GDM prevalence (1999 WHO x1.5) according to IADPSG	15%	13%
The possibility of patient with GDM to receive treatment	90%	80%
(Basal) outcome risk in those not GDM according to WHO and not receiving treatment		
LGA newborn	9%	8.5%
Preeclampsia	4.5%	2.9%
Delivery by cesarean	18.5%	10%
Relative outcome risk in those meeting GDM criteria according to WHO		
LGA newborn	1.53	1.39
Preeclampsia	1.69	1.31
Delivery by cesarean	1.37	1.24
(Basal) outcome risk in those not GDM according to IADPSG and not receiving treatment		
LGA newborn	8.75%	8.18%
Preeclampsia	4.42%	2.81%
Delivery by cesarean	18.5%	10%
Relative outcome risk in those meeting GDM criteria according to IADPSG		
LGA newborn	1.73	1.27
Preeclampsia	1.71	1.37
Delivery by cesarean	1.23	1.01
Benefit of GDM treatment (Relative risk)		
LGA newborn	0.57	0.47
Preeclampsia	0.61	0.46
Delivery by cesarean	0.90	0.78

GDM: Gestational diabetes mellitus; **IADPSG:** International Association of the Diabetes and Pregnacy Study Groups; **LGA:** large for gestational age; **WHO:** World Health Organization. Adapted from Falavigna et al.[12]

IADPSG criteria is a little higher than those according to WHO criteria, but the cost efficiency and compliance of sources should be taken into consideration.

While the debates about IADPSG recommendations have been carried on, Werner et al. published a study investigating the basics of GDM screening.[18]

Table 7. When compared to non-screening, the impacts of screening strategies on LGA, preeclampsia and cesarean rates (absolute risk decrease and the number of cases required to have screening).

	No screening	Screening according to 1999 WHO criteria			Screening according to IADPSG criteria		
	Incidence (%) (%95 CI)	Incidence (%) (%95 CI)	ARR (%) (%95 CI)	NNS (%95 CI)	Incidence (%) (%95 CI)	ARR (%) (%95 CI)	NNS (%95 CI)
Main model							
LGA newborn	9.48 (8.98-9.98)	8.95 (8.43-9.41)	0.53 (0.37-0.74)	189 (134-268)	8.63 (7.99-9.16)	0.85 (0.54-1.29)	117 (77-185)
Preeclampsia	4.81 (2.96-6.81)	4.54 (2.79-6.44)	0.27 (0.10-0.45)	376 (223-1010)	4.42 (2.70-6.27)	0.39 (0.15-0.65)	257 (154-679)
Delivery by cesarean	19.18 (9.83-29.15)	18.93 (9.74-28.85)	0.25 (0.12 - 0.60)	399 (165-848)	18.84 (9.68-28.71)	0.34 (0.16 - 0.83)	296 (120-622)
Model with HAPO criteria							
LGA newborn	9.57	8.97 (8.74-9.14)	0.60 (0.43-0.83)	167 (120-231)	8.57 (8.19-8.85)	1.00 (0.72-1.38)	100 (77-185)
Preeclampsia	5.22	4.92 (4.79-5.06)	0.30 (0.16-0.43)	331 (232-633)	4.71 (4.49-4.95)	0.51 (0.27-0.73)	196 (137-374)
Delivery by cesarean	18	17.74 (17.4-18.11)	0.26 (0.11-0.60)	383 (167-944)	17.63 (17.15-8.15)	0.37 (0.15-0.85)	272 (118-669)

ARR: absolute risk reduction; **CI:** credible interval; **DSÖ:** Dünya Sağlık Örgütü; **HAPO:** Hyperglycemia and Adverse Pregnancy Outcomes Study; **IADPSG:** International Association of Diabetes in Pregnancy Study Groups; **LGA:** large for gestational age; **NNS:** number needed to screen. Adapted from Falavigna et al.[12]

Table 8. The impact of various strategies on perinatal outcomes.

	In DM group	In GDM group according to CC	In GDM group according to IADPSG	In euglycemic population
Preeclampsia	20.4%	8.9%	5.8%	4.8%
Shoulder dystocia	5%	2.7%	1.5%	1.3%

Adapted from Werner et al.[18]

Accordingly, three strategies about GDM screening in pregnancy were compared:

- **Strategy 1:** No screening for GDM
- **Strategy 2:** 50-g screening according to Carpenter-Coustan (CC) criteria
- **Strategy 3:** Screening according to IADPSG criteria

When the authors were comparing these models, they calculated that pregestational DM rate was 1.6% in the population they studied, GDM rate according to CC criteria was 3.8%, and GDM rate according to IADPSG criteria (cGDM+iGDM) was 16.2%. While the rates of preeclampsia and should dystocia increased in the pregestational DM group 4-5 times more than euglycemic population, it was found that this increase was about 2 times according to CC criteria, and more moderate (about 10-20%) according to IADPSG criteria (**Table 8**). In terms of the cost-efficiency, it was reported that 34% of the cGDM cases would turn into overt DM, 25.7% of the iGDM cases would turn into overt DM within 15 years. Diabetes Prevention Programs have reported that the transition of the group at high risk to the overt DM within a period more than 10 years can be decreased up to 34% by intensive life-style modifications, and that the decrease may reach up to 53% in GDM cases. According to the estimations of researchers by taking into account all these, in a population of 100,000 cases, 56 cases with shoulder dystocia (995 cases instead of 1051 cases) can be prevented by screening and treating according to CC criteria and additional 85 cases (910 cases instead of 995 cases) can be prevented by screening according to IADPSG criteria; however, in order to manage to do this, it is required to spend 38,768,139 USD according to CC criteria, and 125,633,826 USD more for IADPSG criteria in addition to CC criteria (**Table 9**).

It was estimated that the periodical screenings in further periods of women who are diagnosed as GDM in their pregnancies, their inclusion to the Diabetes Prevention Programs, life-style changes, diet, and insulin-sensitizing drugs etc. may provide 6178 quality adjusted life years (QALY). The authors concluded in their study that screening according to IADPSG criteria may be cost-effective if efforts are made to prevent overt DM in the long-term.[18]

Table 9. Cost-benefit analysis of GDM screening strategies for 100,000 individuals.

	Strategy 1	Strategy 2	Strategy 3	Difference between Strategies 2 and 3
Number of cases diagnosed as GDM	0	5020	17,800	12,780
Number of DM cases in further periods which can be prevented by intervention	0	446	1134	688
Shoulder dystocia	1051	995	910	85
Number of preeclampsia cases	5292	5074	4812	262
Total QALY	5,563,323	5,565,646	5,571,824	6178
Total cost (ABD $, 2011)	831,622,028	870,390,167	996,023,993	125,633,826
Marginal cost/gained QALY*	-	16.689	20.336	-
If GDM diagnosis is not used for maternal benefit in the long-term				
Total QALY	5,563,323	5,563,340	5,563,367	27
Total cost (ABD $, 2011)	831,622,028	840,855,046	856,121,038	15,265,992
Marginal cost/gained QALY*	-	543,119	565,407	-

GDM: gestational diabetes mellitus; **QALY:** quality adjusted life years; **Strategy 1:** Non-screening, **Strategy 2:** Current approach, **Strategy 3:** Approach according to IADPSG recommendations. ***:** When Strategy 2 is compared to Strategy 1, and Strategy 3 compared to Strategy 2. Adapted from Werner et al.[18]

Current data shows that many gestational complications can be decreased and perinatal outcomes can be improved by GDM screening and treatment. Therefore, diabetic screening in pregnancy is recommended in many countries and by WHO. The sensitivities of the tests, depending on the threshold values used, vary between 80% and 90%. The results of HAPO study report that increased perinatal risks also continue in cases considered as normal by current criteria. IADPSG reviewed the results of HAPO study in detail, and recommended new threshold values for 75-g single-step OGTT. There has been still no randomized controlled study about the benefits and costs for putting the recommendations of IADPSG into practice. Current data show that GDM prevalence will increase about 3 times (15-20%) in case of GDM diagnosis according to IADPSG criteria. This also means the increase of costs. The dominance on screening procedures and treatments by current methods and the benefit of this cost increase in all societies have not been presented yet in terms of perinatal outcomes. A cost-benefit analysis carried out on this matter suggests that there is no significant benefit of screening according to IADPSG in terms of perinatal outcomes. However, if utilized in an effective way in the plans for further periods of GDM cases, it is considered that IADPSG recommendations may be cost-effective. As of today, there is no sufficient data to initiate the practices of IADPSG criteria in order to improve perinatal outcomes in terms of universal screening. Randomized controlled studies to be performed will be helpful to clarify the situation.

Conflicts of Interest: No conflicts declared.

References

1. Metzger BE, Coustan DR. Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. The Organizing Committee. Diabetes Care 1998;21 Suppl 2:B161-7.
2. Xiong X, Saunders LD, Wang FL, Demianczuk NN. Gestational diabetes mellitus: prevalence, risk factors, maternal and infant outcomes. Int J Gynaecol Obstet 2001;75:221-8.
3. Landon MB, Vickers S. Fetal surveillance in pregnancy complicated by diabetes mellitus: is it necessary? J Matern Fetal Neonatal Med 2002;6:413-6.
4. 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.
5. 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.
6. Alwan N, Tuffnell DJ, West J. Treatments for gestational diabetes. Cochrane Database Syst Rev 2009;3:CD003395.
7. Donovan L, Hartling L, Muise M, Guthrie A, Vandermeer B, Dryden DM. Screening tests for gestational diabetes: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2013;159:115-229.
8. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991-2002.
9. International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, et al. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;3:676-82.
10. Bodmer-Roy S, Morin L, Cousineau J, Rey E. Pregnancy outcomes in women with and without gestational diabetes mellitus according to the International Association of the Diabetes and Pregnancy Study Groups criteria. Obstet Gynecol 2012;4: 746-52.
11. Wendland EM, Torloni MR, Falavigna M, Trujillo J, Dode MA, Campos MA, et al. Gestational diabetes and pregnancy outcomes - a systematic review of the World Health Organization (WHO) and the International Association of Diabetes in Pregnancy Study Groups (IADPSG) diagnostic criteria. BMC Pregnancy Childbirth 2012;12:23.
12. Falavigna M, Prestes I, Schmidt MI, Duncan BB, Colagiuri S, Roglic G. Impact of gestational diabetes mellitus screening strategies on perinatal outcomes: a simulation study. Diabetes Res Clin Pract 2013;99:358-65.
13. Schmidt MI, Duncan BB, Reichelt AJ, Branchtein L, Matos MC, Forti Costa e, Spichler ER, Pousada JM, Teixeira MM, Yamashita T: Gestational diabetes mellitus diagnosed with a 2-h 75-g oral glucose tolerance test and adverse pregnancy outcomes. Diabetes Care 2001;24:1151-5.
14. Black MH, Sacks DA, Xiang AH, Lawrence JM: Clinical outcomes of pregnancies complicated by mild gestational diabetes mellitus differ by combinations of abnormal oral glucose tolerance test values. Diabetes Care 2010;33:2524-30.
15. Khan KS, Syed AH, Hashmi FA, Rizvi JH: Relationship of fetal macrosomia to a 75 g glucose challenge test in nondiabetic pregnant women. Aust N Z J Obstet Gynaecol 1994;34:24-7.
16. Sugaya A, Sugiyama T, Nagata M, Toyoda N: Comparison of the validity of the criteria for gestational diabetes mellitus by WHO and by the Japan Society of Obstetrics and Gynecology by the outcomes of pregnancy. Diabetes Res Clin Pract 2000;50:57-63.
17. Aberg A, Rydhstroem H, Frid A: Impaired glucose tolerance associated with adverse pregnancy outcome: a population-based study in southern Sweden. Am J Obstet Gynecol 2001;184:77-83.
18. Werner EF, Pettker CM, Zuckerwise L, Reel M, Funai EF, Henderson J, et al. Screening for gestational diabetes mellitus: are the criteria proposed by the international association of the Diabetes and Pregnancy Study Groups cost-effective? Diabetes Care 2012;35:529-35.