IADPSG and WHO 2013 Gestational Diabetes Mellitus Criteria Identify Obese Women With Marked Insulin Resistance in Early Pregnancy

Jürgen Harreiter,[1] David Simmons,[2] Gernot Desoye,[3] Rosa Corcoy,[4,5] Juan M. Adelantado,[4] Roland Devlieger,[6,7,8] Andre van Assche,[6] Sander Galjaard,[6,7,9] Peter Damm,[10] Elisabeth R. Mathiesen,[10] Dorte M. Jensen,[11,12] Lise Lotte T. Andersen,[12] Fidelma Dunne,[13] Annunziata Lapolla,[14] Maria G. Dalfra,[14] Alessandra Bertolotto,[15] Urzula Mantaj,[16] Ewa Wender-Ozegowska,[16] Agnieszka Zawiejska,[16] David Hill,[17] Judith G.M. Jelsma,[18] Frank J. Snoek,[19] Christof Worda,[20] Dagmar Bancher-Todesca,[20] Mireille N.M. van Poppel,[18,21] and Alexandra Kautzky-Willer,[1] on behalf of the DALI Core Investigator group

Implementation of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) and the World Health Organization 2013 (WHO 2013) recommendations leads to an increased prevalence of gestational diabetes mellitus (GDM) due to more stringent criteria and early screening of women at high risk for diabetes in pregnancy (DIP) (1,2). IADPSG members now recommend that their GDM criteria should not be used in early pregnancy but have not provided alternative criteria (3). We have compared the characteristics of overweight/obese women early in pregnancy, with and without GDM using the new criteria, to assess whether those testing positive are metabolically distinct.

Pregnant women with a BMI $\geq 29.0 \, \text{kg/m}^2$ underwent a 75-g oral glucose tolerance test in early pregnancy as part of enrollment into the DALI (Vitamin D And Lifestyle Intervention for GDM prevention) pilot and lifestyle Pan-European multicenter trials (4). GDM and DIP were diagnosed using WHO 2013 criteria.

A high rate of GDM (237/1,035 or 22.9%: DIP 0.5%; total hyperglycemia in early pregnancy 23.4%) was found at a mean of 15.2 ± 3.0 gestational weeks (interquartile range 13.4–16.8).

A fasting glucose alone identified 190/242 (78.5%) women. The other 52 women (21.5%) were diagnosed with elevated

[1]Gender Medicine Unit, Division of Endocrinology and Metabolism, Department of Medicine III, Medical University of Vienna, Vienna, Austria
[2]Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, England and Macarthur Clinical School, Western Sydney University, Sydney, Australia
[3]Department of Obstetrics and Gynecology, Medizinische Universitaet Graz, Graz, Austria
[4]Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
[5]CIBER Bioengineering, Biomaterials and Nanomedicine, Instituto de Salud Carlos III, Zaragoza, Spain
[6]Department of Development and Regeneration, KU Leuven, Leuven, Belgium
[7]Department of Obstetrics and Gynecology, University Hospitals Leuven, Leuven, Belgium
[8]Department of Obstetrics, Gynecology and Fertility, GasthuisZusters Antwerpen Sint-Augustinus, Wilrijk, Belgium
[9]Department of Obstetrics and Gynaecology, Division of Obstetrics and Prenatal Medicine, Erasmus MC, University Medical Centre, Rotterdam, the Netherlands
[10]Center for Pregnant Women with Diabetes, Departments of Endocrinology and Obstetrics, Rigshospitalet and The Clinical Institute of Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[11]Department of Endocrinology, Odense University Hospital, Odense, Denmark
[12]Department of Gynaecology and Obstetrics, Odense University Hospital and Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark
[13]Galway Diabetes Research Centre (GDRC) and National University of Ireland, Galway, Ireland
[14]Università degli Studi di Padova, Padua, Italy
[15]Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy
[16]Medical Faculty I, Poznan University of Medical Sciences, Poznan, Poland
[17]Recherche en Santé Lawson SA, St. Gallen, Switzerland
[18]Department of Public and Occupational Health, EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, the Netherlands
[19]Department of Medical Psychology, EMGO Institute for Health and Care Research, VU University Medical Center, and Medical Psychology Academic Medical Center, Amsterdam, the Netherlands
[20]Division of Obstetrics and Feto-Maternal Medicine, Department of Obstetrics and Gynecology, Medical University of Vienna, Vienna, Austria
[21]Institute of Sports Sciences, University of Graz, Graz, Austria

Corresponding author: Alexandra Kautzky-Willer, alexandra.kautzky-willer@meduniwien.ac.at.

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Table 1—Descriptive analysis, surrogate parameters of insulin sensitivity, insulin secretion, and metabolic parameters of DALI pilot and lifestyle study population in early pregnancy

	NGT (total N = 793)		Early GDM (total N = 237)		DIP (total N = 5)		
	n	Mean ± SD or %	n	Mean ± SD or %	n	Mean ± SD or %	P (NGT vs. GDM)
Age (years)	780	31.9 ± 5.3	230	32.8 ± 5.1	5	31.7 ± 3.7	**0.04**
Height (cm)	778	165.5 ± 6.8	227	165.7 ± 6.2	5	163.1 ± 1.2	0.75
Prepregnancy weight (kg)	780	92.4 ± 13.8	228	96.9 ± 16.1	5	93.3 ± 15.4	**<0.001**
Prepregnancy BMI (kg/m^2)	777	33.7 ± 4.3	222	35.2 ± 5.3	5	35.0 ± 5.3	**<0.001**
BMI at screening (kg/m^2)	778	34.4 ± 4.3	226	36.1 ± 5.6	5	35.6 ± 4.9	**<0.001**
Weight gain until first visit (kg)*	778	2.0 ± 4.4	221	2.5 ± 7.8	5	1.7 ± 4.1	0.25
Gestational age (weeks)	779	15.2 ± 3.1	228	15.0 ± 2.4	5	13.4 ± 4.3	0.36
Waist circumference (cm)	764	107.2 ± 10.4	219	110.3 ± 11.6	5	109.4 ± 9.7	**<0.001**
Sum of skinfolds (mm)	763	107.6 ± 28.1	217	114.8 ± 30.7	5	104.6 ± 11.9	**0.001**
European descent	674/778	86.6%	195/225	86.7%	1/5	20.0%	1.00
Higher education	431/777	55.5%	121/223	54.3%	3/5	60.0%	0.81
Lives with partner	730/777	94.0%	203/221	91.9%	4/5	80.0%	0.28
Smoking	132/781	16.9%	34/237	14.3%	0/5	0%	0.37
Alcohol consumption	46/781	5.9%	7/237	3.0%	0/5	0%	0.09
Multiparity	389/777	50.1%	110/224	49.1%	1/5	20%	0.82
Diabetes in family	185/781	23.7%	64/237	27.0%	3/5	60.0%	0.30
History of GDM	38/483	7.9%	22/137	16.1%	1/2	50.0%	**0.01**
Previous stillbirth	49/480	10.2%	19/140	13.6%	1/2	50.0%	0.28
Previous macrosomia	86/480	17.9%	44/138	31.9%	0/2	0%	**0.001**
Previous congenital malformation	16/482	3.3%	9/139	6.5%	0/2	0%	0.14
Previous chronic hypertension	99/772	12.8%	31/222	14.0%	0/5	0%	0.74
Systolic blood pressure (mmHg)	778	116.4 ± 11.1	225	118.3 ± 10.1	5	123.6 ± 7.0	**0.02**
Diastolic blood pressure (mmHg)	778	72.8 ± 9.2	225	75.1 ± 8.4	5	78.2 ± 6.8	**0.001**
Heart rate (bpm)	738	79.4 ± 10.0	206	82.0 ± 10.6	5	79.2 ± 9.4	**0.001**
FPG (mmol/L)	713	4.6 ± 0.4	215	5.1 ± 0.6	5	6.2 ± 1.1	**<0.001**
1-h plasma glucose (mmol/L)	669	6.7 ± 1.4	201	8.5 ± 2.0	4	12.4 ± 1.7	**<0.001**
2-h plasma glucose (mmol/L)	670	5.8 ± 1.1	200	7.0 ± 1.6	5	9.0 ± 3.3	**<0.001**
Fasting insulin (mU/L)	706	14.9 ± 11.6	209	18.8 ± 9.0	5	32.1 ± 26.5	**<0.001**
1-h insulin (mU/L)	656	107.7 ± 73.4	194	148.2 ± 90.5	5	149.6 ± 107.9	**<0.001**
2-h insulin (mU/L)	656	76.2 ± 59.1	196	121.9 ± 97.5	5	187.3 ± 195.7	**<0.001**
AUC glucose (mmol/L)	665	12.3 ± 1.9	200	14.9 ± 2.7	4	20.5 ± 2.8	**<0.001**
AUC insulin (mU/L)	647	164.8 ± 94.6	193	226.1 ± 129.9	3	347.6 ± 231.1	**<0.001**
HOMA IR**	702	3.1 ± 2.9	208	4.3 ± 2.2	5	9.3 ± 8.9	<0.001
QUICKI	702	0.33 ± 0.03	208	0.31 ± 0.02	5	0.29 ± 0.03	**<0.001**
OGIS (mL/min/m^2)	358	424.8 ± 69.0	72	338.9 ± 65.7	0	N/A†	**<0.001**
Matsuda index**	644	4.8 ± 3.5	192	2.9 ± 2.1	5	1.8 ± 1.0	**<0.001**
IGI**	339	2.5 ± 3.2	73	2.1 ± 3.3	0	N/A†	0.32
DI**	328	8.0 ± 8.6	69	3.6 ± 3.8	0	N/A†	**<0.001**
Stumvoll first phase**	647	794.4 ± 802.8	192	1151.6 ± 1063.4	4	901.6 ± 1,804.4	**<0.001**
Stumvoll second phase**	647	505.8 ± 196.4	192	597.9 ± 260.9	4	547.2 ± 437.2	**<0.001**
Plasma leptin (ng/mL)	687	36.8 ± 18.5	206	38.7 ± 19.5	5	52.8 ± 16.2	0.22
Triglycerides (mmol/L)	257	1.32 ± 0.44	99	1.52 ± 0.58	4	1.39 ± 0.58	**0.002**
FFA (mmol/L)	357	0.67 ± 0.24	99	0.74 ± 0.24	4	0.60 ± 0.29	**0.01**
LDL (mmol/L)	357	2.90 ± 0.75	99	2.99 ± 1.01	4	2.58 ± 0.51	0.80
HDL (mmol/L)	356	1.46 ± 0.28	99	1.45 ± 0.30	4	1.21 ± 0.07	0.30
3-β-Hydroxybutyrate (mmol/L)	357	0.08 ± 0.08	99	0.11 ± 0.08	4	0.05 ± 0.06	**0.01**

AUC, area under the curve; DI, disposition index; FFA, free fatty acids; FPG, fasting plasma glucose; HOMA IR, HOMA of insulin resistance (product of fasting plasma insulin and FPG divided by the constant 22.5); IGI, insulinogenic index; NGT, normal glucose tolerant; OGIS, oral glucose insulin sensitivity index; PIH, pregnancy-induced hypertension; QUICKI, quantitative insulin sensitivity check index. Boldface type indicates statistical significance. *Weight gain prepregnancy to first study visit. **Analysis after logarithmic transformation. †Oral glucose tolerance test (30- or 90-min) values missing for calculation.

1-h and/or 2-h glucose levels. Obese women with DIP were less likely to be of European ancestry than women with early GDM (20.0% vs. 86.7%, P = 0.002).

Women with early GDM had significantly greater insulin resistance and higher BMI, waist circumference, systolic and diastolic blood pressures, triglycerides, free fatty acids, 3-β-hydroxybutyrate, and heart rate at screening (Table 1). Significant differences in insulin secretion and disposition index were also found. Differences persisted after adjustment for age, pregestational BMI, gestational week, and fetal sex.

In multivariate logistic regression analyses, which also included gestational week, educational level, and employment status, early GDM was significantly more common with higher prepregnancy BMI (kg/m^2; odds ratio [OR] 1.05, 95% CI 1.00–1.10, P < 0.04), sum of skinfolds in early pregnancy (mm; OR 1.01, 95% CI 1.00–1.02, P < 0.01), prior history of GDM (OR 2.74, 95% CI 1.66–4.50, P < 0.001), and previous macrosomia (OR 1.97, 95% CI 1.03–3.98, P < 0.04). Nulliparity was found to be protective (OR 0.51, 95% CI 0.30–0.86, P < 0.01). In a subanalysis of nulliparous women, multivariate logistic regression found that higher prepregnancy BMI was the only risk factor (OR 1.09, 95% CI 1.03–1.15, P < 0.01) for an early GDM diagnosis.

Although the new criteria have not been validated in early pregnancy, their use in our DALI cohort has identified a profile akin to the metabolic syndrome (5). Prepregnancy BMI was a significant predictor of early GDM and the only predictor among nulliparous women in spite of the cohort only including women with a BMI ≥29.0 kg/m^2. This supports the need for weight control before and after pregnancy. On the basis of these data, we suggest that dropping the IADPSG criteria for GDM diagnosis early in pregnancy may be premature. Continuing their use would provide criteria for GDM early in pregnancy and maintain common criteria throughout pregnancy. How such women are managed should be tested in a randomized controlled trial of immediate GDM treatment versus usual care and to explore the impact on perinatal outcome.

References

1. Metzger BE, Gabbe SG, Persson B, et al.; International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010; 33:676–682
2. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization guideline. Diabetes Res Clin Pract 2014; 103:341–363
3. McIntyre HD, Sacks DA, Barbour LA, et al. Issues with the diagnosis and classification of hyperglycemia in early pregnancy. Diabetes Care 2016;39:53–54
4. Simmons D, Jelsma JGM, Galjaard S, et al. Results from a European multicenter randomized trial of physical activity and/or healthy eating to reduce the risk of gestational diabetes mellitus: the DALI lifestyle pilot. Diabetes Care 2015;38:1650–1656
5. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539–553