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Abstract The objective of this study was to examine measures of insulin resistance and beta cell function in relation to ethnicity and the development of diabetes after gestational diabetes mellitus (GDM). Glucose homeostasis was assessed during a 75 g oral glucose tolerance test 1–2 years after delivery in 456 women with previous GDM (362 European, 94 non-European; including 41 Arab and 43 Asian women) and 133 control women. Insulin resistance was estimated using homeostasis model assessment of insulin resistance (HOMA-IR). The insulinogenic index (I/G30) and the disposition index ([I/G30]/HOMA-IR) were used to quantify insulin secretion. Women developing diabetes after GDM were characterized by increased HOMA-IR (p=0.010, adjusted for BMI), whereas the disposition index was decreased in all women with previous GDM irrespective of glucose tolerance, most pronounced in the presence of diabetes (BMI-adjusted $p=1\cdot10^{-5}$). Non-European origin was associated with increased HOMA-IR (p=0.001 vs. European), strengthened by adjustment for BMI in Asian women (p=0.046 vs. p=0.016), but eradicated among Arab women (p=0.004 vs. p=0.65). Non-European women exhibited an increased frequency of diabetes after GDM (17% vs. European 4%, $p=2\cdot10^{-5}$). In addition to BMI, non-European and Asian origin was associated with the development of diabetes after GDM in a multivariate logistic regression analysis, whereas Arab origin was not. Our results highlight the importance of preventive measures to ensure a healthy lifestyle in women with GDM, particularly in high-risk ethnic groups**.**

Key words Beta cell dysfunction; Ethnicity; Gestational diabetes mellitus; Insulin resistance; OGTT; Postpartum diabetes

Introduction

Gestational diabetes mellitus (GDM) is characterized by insulin resistance and an inability of the beta cells to compensate by sufficient increase in insulin secretion [1]. Although glucose tolerance usually reverts to normal after delivery, the risk of developing type 2 diabetes following GDM is increased [2], with a cumulative incidence of 30–50% within five to ten years after delivery [3,4].

Ethnicity influences the prevalence of GDM and its progression to manifest diabetes postpartum, being higher in non-European populations [5-8]. This may partly be explained by differences in insulin secretion and action [9-13]. We have previously shown that Arab women with GDM are more insulin resistant during pregnancy than Scandinavian women [14]. This finding stimulated our interest in further studies. Understanding the basis of these differences may have clinical implications in the management of GDM and screening strategies for diabetes after pregnancy.

The aims of the present study were to evaluate glucose homeostasis after GDM and to investigate the impact of ethnicity and other determinants of glucose tolerance postpartum.

Material and methods

Study population

The present study was part of the 1–2-year follow-up programme in the Mamma Study, described in detail previously [15]. Briefly, during the years 2003–2005 pregnant women in southern Sweden were invited to take part in a 5-year postpartum follow-up programme. A 75 g

oral glucose tolerance test (OGTT) was offered to all women in the 28th week of gestation, and also in gestational week 12 if they had a history of GDM in previous pregnancies, or a first-degree relative with diabetes. The diagnostic criteria for GDM were those recommended by the WHO, defining GDM as the joint category of diabetes and impaired glucose tolerance (IGT) in non-pregnant adults [16].

At the first follow-up appointment 1–2 years after delivery, an OGTT was performed after overnight fasting in 470 women with previous GDM and 166 women with normal glucose tolerance (NGT) during pregnancy. Venous samples were drawn at 0, 30 and 120 min to determine plasma glucose and serum insulin concentrations. Glucose concentration was measured in duplicate samples and the mean value calculated. Weight and height were recorded, and the body mass index (BMI) calculated. Information was obtained on family history of diabetes, earlier pregnancies and ethnic affiliation. Based on the stated country of origin of at least three grandparents, women with previous GDM were grouped into European (*n*=362) and non-European (*n*=94) origin. The latter included subgroups of Arab women (*n*=41: Egypt, Iraq, Lebanon, Morocco, Palestine, Somalia, Syria), Asian women (*n*=43: Afghanistan, China, India, Iran, Japan, Kurdistan, Pakistan, Philippines, South Korea, Taiwan, Thailand, Turkey, Vietnam) and other origins (*n*=10: Berber, Bolivia, Brazil, Chile, Colombia, Eritrea, Ghana, Israel, Uganda, Uruguay). Using the definition described above 14 women were unclassifiable.

Diagnostic criteria were those proposed by the WHO [16]. Informed consent was obtained from all participants, and the study protocol was approved by the Ethics Committee of Lund University (LU 259-00).

Metabolic measurements

The HemoCue Glucose 201+ system (HemoCue AB, Ängelholm, Sweden) was used for immediate measurement of plasma glucose concentrations (mmol/l). Mean coefficient of

variation (CV) of the duplicate analyses performed in this study was 2.2 %. Serum insulin concentrations (mU/l) were measured with an enzyme-linked immunosorbent assay (Dako, Glostrup, Denmark). The intra- and inter-assay CVs of this insulin assay is 5.1–7.5% and 4.2–9.3%, respectively. Homeostasis model assessment was used to estimate insulin resistance (HOMA-IR), i.e. fasting serum insulin x fasting plasma glucose/22.5 [17,18]. Beta cell function was estimated using the insulinogenic index (I/G30), which is the ratio of the incremental insulin to glucose during the first 30 min of the OGTT, i.e. (insulin 30 min – insulin 0 min)/(glucose 30 min – glucose 0 min) [19]. As insulin resistance modulates insulin secretion the disposition index was used to adjust insulin secretion for the degree of insulin resistance, obtained by dividing I/G30 by HOMA-IR [9].

Statistical analyses

Data are presented as *n* (%) and the median (95% confidence interval [CI]). Indices, requiring log transformation, are presented as geometric means (95% CI). Differences between medians were tested using the Mann-Whitey U-test, and differences in geometric means with analysis of variance (ANOVA), incorporating, when appropriate, age, non-European origin, first-degree diabetes heredity, number of deliveries and interval to follow-up as covariates, with and without adjustment for BMI. Fisher's exact test was used to compare group frequencies. Univariate logistic regression analysis was applied to calculate the odds ratios (OR) (95% CI) for diabetes vs. NGT after GDM. Multivariate logistic regression analysis was used to show how known predictor variables affected the risk of developing diabetes after GDM. Variables tested for associations with diabetes after GDM were age (years), BMI (kg/m^2), first-degree relative(s) with diabetes (yes/no), non-European, Arab or Asian origin (yes/no) and parity, which was best expressed as up to three deliveries at follow-up vs. more than three (≤3/>3). European origin was used as a reference for ethnic comparison. All logistic regressions were adjusted for time to

follow-up (days). IBM SPSS Statistics 20 for Windows (IBM Corporation, New York, NY, USA) was used for analysis. Two-sided *p*-values of less than 0.05 were considered statistically significant.

Results

Table 1 presents data describing the study groups and the results of the main outcome measures. Women with previous GDM were grouped according to glucose tolerance at follow-up. Of the 166 women with NGT during pregnancy, 133 also had NGT at follow-up and served as controls. Adjustments were made in the main analyses for observed differences in demographic variables, with and without BMI as a covariate. Compared with the controls, HOMA-IR was increased after GDM among women with diabetes, even when adjusted for BMI. Increased HOMA-IR was also noted among women with IFG after GDM. Beta cell function, measured as the insulinogenic index, was lower among women with previous GDM than in controls, and was related to glucose tolerance, being lowest among those who had diabetes. These differences were even more pronounced when adjusting the insulinogenic index for insulin resistance in the disposition index.

Table 2 gives the results of the main outcome measures in women with previous GDM, grouped according to ethnicity. No differences were found between women from Western and Eastern Europe, and they were therefore grouped together. Non-European, Arab and Asian origin, was associated with higher HOMA-IR than European origin. Arab women were more overweight than European women, who had similar BMIs to Asian women. It is noteworthy that after adjustment for BMI, HOMA-IR did not differ between Arab and European women, whereas the difference was more pronounced among Asian women. Beta cell function, measured as the insulinogenic index, was unaffected by ethnicity. However, when adjusting for the degree

of insulin resistance in the disposition index non-European women showed lower estimates of beta cell function.

The frequency of diabetes after GDM was higher in all non-European groups than in European women. Among European women, 13/362 (4%) were diagnosed with diabetes, compared to 16/94 (17%) among non-European women ($p=2\cdot10^{-5}$). The corresponding numbers for Arab women were 7/41 (17%) ($p=0.002$), and for Asian women 6/43 (14%) ($p=0.010$). Among Arab women the diagnosis in three women was based on the fasting value alone, and that of four women on the 2-hour value alone. Among Asian women the diagnosis in one woman was based on the fasting value alone, and that of five women on the 2-hour value alone.

The results of the logistic regression analyses are presented in Table 3. All analyses were adjusted for time to follow-up visit. Of the variables tested, using univariate analyses, for an association with diabetes after GDM, BMI and the different categories of non-European ethnicity showed the highest associations. In the final multivariate model, in which all the selected predictors of diabetes development after GDM were assessed in separate analyses for the different ethnic groups, BMI showed the highest association. Additionally, non-European and Asian origin showed significant associations, whereas Arab origin did not.

Discussion

To the best of our knowledge, this is the first study evaluating indices of insulin resistance and beta cell function during OGTT after GDM in relation to ethnicity. The key findings were that women of non-European origin were more insulin resistant than European women and exhibited a higher frequency of diabetes. The effect of ethnicity on insulin resistance was more pronounced in Asian women after adjustment for BMI but eradicated among Arab women. In

addition to BMI, Asian ethnicity was associated with diabetes after GDM, whereas Arab origin was not.

The strength of this study is that measures of beta cell function were derived from the OGTT. HOMA has shown good correlation with more sophisticated measures of insulin sensitivity [20], but does not reveal differences between first- and second-phase insulin release and, therefore, gives a less reliable measure of beta cell function than those obtained during the OGTT [19,21].

A limitation of the study is the relatively small numbers in the non-European groups which did not allow comparisons within the separate ethnic groups with regard to glucose tolerance. Moreover, the available number of samples for calculation of indices of insulin resistance and secretion was limited. Due to these circumstances statistical power could not be obtained to test how ethnicity modulates these measures in relation to diabetes development.

When comparing the different glucose categories in the group of women with previous GDM with the controls, and adjusting for ethnicity and other known predictor variables [22], the development of diabetes was associated with increased insulin resistance. Furthermore, decreased beta cell function seemed to be an important contributor to the impairment of glucose tolerance. As opposed to women with IGT, women with IFG had higher HOMA-IR than controls. When adjusting the insulinogenic index for HOMA-IR in the disposition index, beta cell function was similarly affected in women with IFG and IGT. These findings are consistent with previously published results [23,24]. DeFronzo and colleagues compared the presence of impaired insulin secretion and insulin resistance in individuals with IFG and IGT, as defined by the ADA criteria, using the OGTT and the hyperinsulinemic clamp [23]. When HOMA-IR was used to derive an index of insulin resistance, IFG subjects were found to be markedly insulin resistant compared with subjects with NGT, while subjects with IGT had minimally (not significantly) reduced insulin sensitivity. Using the insulin clamp-derived measurement of insulin resistance, individuals with IFG were primarily characterized by hepatic insulin

resistance, while subjects with IGT mainly had muscle insulin resistance. Insulin secretion, measured by the ratio of the area under the insulin to the glucose curve during the OGTT, was reduced similarly in subjects with IFG and IGT. To further characterize the defect in beta cell function in IFG they used the hyperglycemic clamp [24]. When adjusted for the prevailing level of insulin resistance, first-phase insulin secretion was markedly decreased in both IFG and IGT, whereas second-phase insulin secretion was decreased only in IGT.

Kousta et al. [11] used a similar approach as we did to evaluate glucose regulation and other features of the metabolic syndrome 1–2 years postpartum in women with previous GDM. When comparing women with abnormal glucose tolerance to those with normal glucose values and controls they found similar results to ours, with the exception that women with normal glucose values had higher basal insulin secretion than the other groups, indicating an ability to compensate for the concomitant insulin resistance. However, beta cell function was obtained by HOMA in the fasting state and was therefore less accurate [19]. Moreover, glucose tolerance was based on OGTTs in only a subset of the women.

Our results are supported by a study by Jensen et al. [9], who evaluated insulin resistance and beta cell function during OGTT in a large number of subjects in the US who were first-degree relatives of individuals with type 2 diabetes, representing four ethnic groups (African-American, Asian-American, Hispanic-American and Caucasian). They found similar patterns of progressively increasing insulin resistance and decreasing beta cell function with decreasing glucose tolerance among all ethnic groups, suggesting similar pathogenesis of type 2 diabetes across ethnicity.

In the present study, Arab women were characterized by insulin resistance, which, in contrast to our previous findings [14], was no longer apparent after adjustment for BMI. The results of these two studies are not completely comparable since a higher 2-hour cut-off was used in the previous study to define GDM, and furthermore, it was based on data obtained during pregnancy, i.e. during an extremely insulin-resistant state. Gunton et al. evaluated HOMA

indices in a group of pregnant women in Australia and found that Arab women with GDM were more insulin resistant than Asian and Caucasian women, and had a higher BMI than Asian women, although no adjustments were made for BMI [10]. Furthermore, GDM was associated with a similar trend to lower beta cell function in all ethnic groups. In a recent study, Morkrid et al. assessed changes in insulin resistance and beta cell function by HOMA in a multi-ethnic cohort of women living in Norway [13]. They reported results similar to ours. Regardless of glucose tolerance, they found that Middle Eastern, South Asian (mainly Pakistan and Sri Lankan) and East Asian (mainly Vietnamese and Philippine) women were more insulin resistant than Western European women in early gestation. The difference in HOMA-IR did not persist after adjustment for BMI in Middle Eastern women, but was still present in Asian women, and strengthened for the East Asian group. The increase in insulin resistance from early to late gestation was similar across the ethnic groups, but the increase in beta cell function was significantly lower in East and South Asians compared with Western Europeans and did not match the change in insulin resistance.

OGTT-derived insulin sensitivity index (OGIS) may provide further information with regard to ethnic differences. OGIS correlates strongly with total glucose disposal, as assessed by the glucose clamp, while HOMA-IR mainly reflects changes in hepatic insulin resistance [23,25]. Lapolla et al. evaluated OGTT-derived measures of insulin sensitivity and beta cell function in a large population of normal-weight pregnant women and found that OGIS, but not fasting measurements, was impaired in early pregnancy in women who developed GDM in late pregnancy [26]. However, in late pregnancy both fasting and dynamic indices of insulin sensitivity were decreased in women with GDM, suggesting a possible different glucose handling behavior between the liver and the periphery during the early and late phase of pregnancy. Beta cell impairment, assessed by the ratio of the area under the insulin to the glucose curve, was evident only when GDM was manifest and was characterized by inappropriate adaptation to the pregnancy induced increase in insulin resistance.

Unfortunately, the present material was undersized to evaluate the potential impact of ethnicity on indices of insulin resistance and secretion in the multivariate logistic regression analysis, which limits the study. In fact, these measures showed strong associations with diabetes development in univariate analysis, and when included in the multivariate model they outweighed the effect of most other variables, including ethnicity. Since insulin resistance and impaired beta cell function are closely linked to the pathophysiology of type 2 diabetes this could be expected, and a larger sample size is needed to rule out the possibility of an effect of ethnicity on these measures. For this reason, we decided to rather focus on how ethnicity affects the association between clinical risk factors and the development of diabetes after GDM. Such knowledge may have implications for screening strategies and follow-up of these women.

At comparable BMI, the Asian women in the present study were more insulin resistant than European women and exhibited a higher frequency of diabetes after GDM. When various predictors of the development of postpartum diabetes [22] were assessed in the multivariate logistic regression analysis, BMI also showed the highest association when considering Asian vs. European ethnicity. Epidemiological data indicate that the pathophysiology of diabetes may differ in the Asian population [27]. It has been suggested that lower cut-off values should be used to define overweight and central obesity in the Asian population than in other populations [28,29]. However, no uniform cut-off values have been defined due to the considerable heterogeneity in the Asian population. In this context, it is interesting to note that five of the six women who developed diabetes among the Asian women were diagnosed based on the 2-hour value of the OGTT alone, and only one woman (BMI 42 kg/m^2) on the fasting value alone. Fasting plasma glucose has been reported to be less sensitive for diagnosing diabetes than the 2-hour value in the Asian population, which may lead to misclassification if an OGTT is not performed [27]. This furthermore underlines the importance of performing a 75 g OGTT during pregnancy to detect GDM in the Asian population, particularly when the WHO criteria are applied. However, this approach may not be feasible in all settings. The introduction of the new

IADPSG criteria, providing lower thresholds for GDM than those currently used in most parts of the world, will have a major impact on screening strategies for GDM [30]. A recent study in a high-risk population in the Mediterranean region shows that a combined risk score of fasting plasma glucose concentration ≥5.0 mmol/l, age ≥30 years, pre-pregnancy BMI ≥25 kg/m^2 or third trimester BMI ≥30 kg/m^2, identifies most women with GDM, as defined by the new IADPSG criteria, reducing the need for an OGTT to less than 20% of the pregnant population [31].

In conclusion, the development of diabetes after GDM was associated with insulin resistance, differently modulated by ethnicity and BMI in Arab and Asian women. Furthermore, decreased beta cell function was an important contributor to the impairment of glucose tolerance. Our results highlight the importance of preventive measures to ensure a healthy lifestyle in women with GDM, particularly in high-risk ethnic groups**.**

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Conflict of Interest: None

References

1. Buchanan TA, Xiang A, Kjos SL, Watanabe R (2007) What is gestational diabetes? Diabetes care 30 Suppl 2:S105-111. doi:10.2337/dc07-s201

2. Bellamy L, Casas JP, Hingorani AD, Williams D (2009) Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet 373 (9677):1773-1779. doi:10.1016/S0140-6736(09)60731-5

3. Kim C, Newton KM, Knopp RH (2002) Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes care 25 (10):1862-1868

4. Ekelund M, Shaat N, Almgren P, Groop L, Berntorp K (2010) Prediction of postpartum diabetes in women with gestational diabetes mellitus. Diabetologia 53 (3):452-457. doi:10.1007/s00125-009-1621-3

5. Ben-Haroush A, Yogev Y, Hod M (2004) Epidemiology of gestational diabetes mellitus and its association with Type 2 diabetes. Diabet Med 21 (2):103-113

6. Xiang AH, Li BH, Black MH, Sacks DA, Buchanan TA, Jacobsen SJ, Lawrence JM (2011) Racial and ethnic disparities in diabetes risk after gestational diabetes mellitus. Diabetologia 54 (12):3016-3021. doi:10.1007/s00125-011-2330-2

7. Girgis CM, Gunton JE, Cheung NW (2012) The influence of ethnicity on the development of type 2 diabetes mellitus in women with gestational diabetes: a prospective study and review of the literature. ISRN endocrinology 2012:341638. doi:10.5402/2012/341638

8. Jenum AK, Morkrid K, Sletner L, Vangen S, Torper JL, Nakstad B, Voldner N, Rognerud-Jensen OH, Berntsen S, Mosdol A, Skrivarhaug T, Vardal MH, Holme I, Yajnik CS, Birkeland KI (2012) Impact of ethnicity on gestational diabetes identified with the WHO and the modified International Association of Diabetes and Pregnancy Study Groups criteria: a population-based cohort study. European journal of endocrinology / European Federation of Endocrine Societies 166 (2):317-324. doi:10.1530/EJE-11-0866

9. Jensen CC, Cnop M, Hull RL, Fujimoto WY, Kahn SE, American Diabetes Association GSG (2002) Beta-cell function is a major contributor to oral glucose tolerance in high-risk relatives of four ethnic groups in the U.S. Diabetes 51 (7):2170-2178

10. Gunton JE, Hitchman R, McElduff A (2001) Effects of ethnicity on glucose tolerance, insulin resistance and beta cell function in 223 women with an abnormal glucose challenge test during pregnancy. The Australian & New Zealand journal of obstetrics & gynaecology 41 (2):182-186

11. Kousta E, Efstathiadou Z, Lawrence NJ, Jeffs JA, Godsland IF, Barrett SC, Dore CJ, Penny A, Anyaoku V, Millauer BA, Cela E, Robinson S, McCarthy MI, Johnston DG (2006) The impact of ethnicity on glucose regulation and the metabolic syndrome following gestational diabetes. Diabetologia 49 (1):36-40. doi:10.1007/s00125-005-0058-6

12. Kousta E, Lawrence NJ, Godsland IF, Penny A, Anyaoku V, Millauer BA, Robinson S, Johnston DG, McCarthy MI (2007) Early metabolic defects following gestational diabetes in three ethnic groups of anti-GAD antibodies negative women with normal fasting glucose. Hormones 6 (2):138-147

13. Morkrid K, Jenum AK, Sletner L, Vardal MH, Waage CW, Nakstad B, Vangen S, Birkeland KI (2012) Failure to increase insulin secretory capacity during pregnancy-induced insulin resistance is associated with ethnicity and gestational diabetes. European journal of endocrinology / European Federation of Endocrine Societies 167 (4):579-588. doi:10.1530/EJE-12-0452

14. Shaat N, Ekelund M, Lernmark A, Ivarsson S, Nilsson A, Perfekt R, Berntorp K, Groop L (2004) Genotypic and phenotypic differences between Arabian and Scandinavian women with gestational diabetes mellitus. Diabetologia 47 (5):878-884. doi:10.1007/s00125-004-1388-5

15. Anderberg E, Landin-Olsson M, Kalen J, Frid A, Ursing D, Berntorp K (2011) Prevalence of impaired glucose tolerance and diabetes after gestational diabetes mellitus comparing different cut-off criteria for abnormal glucose tolerance during pregnancy. Acta Obstet Gynecol Scand 90 (11):1252-1258. doi:10.1111/j.1600-0412.2011.01214.x

16. World Health Organization (1999) Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus. WHO Technical Report Series, vol 344. World Health Organization, Geneva

17. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28 (7):412-419

18. Muniyappa R, Lee S, Chen H, Quon MJ (2008) Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. American journal of physiology Endocrinology and metabolism 294 (1):E15-26. doi:10.1152/ajpendo.00645.2007

19. Phillips DI, Clark PM, Hales CN, Osmond C (1994) Understanding oral glucose tolerance: comparison of glucose or insulin measurements during the oral glucose tolerance test with specific measurements of insulin resistance and insulin secretion. Diabet Med 11 (3):286-292

20. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauni T, Muggeo M (2000) Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes care 23 (1):57-63

21. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP, et al. (1993) Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. Diabetes 42 (11):1663-1672

22. Dornhorst A, Rossi M (1998) Risk and prevention of type 2 diabetes in women with gestational diabetes. Diabetes care 21 Suppl 2:B43-49

23. Abdul-Ghani MA, Jenkinson CP, Richardson DK, Tripathy D, DeFronzo RA (2006) Insulin secretion and action in subjects with impaired fasting glucose and impaired glucose tolerance:

results from the Veterans Administration Genetic Epidemiology Study. Diabetes 55 (5):1430-1435

24. Kanat M, Mari A, Norton L, Winnier D, DeFronzo RA, Jenkinson C, Abdul-Ghani MA (2012) Distinct beta-cell defects in impaired fasting glucose and impaired glucose tolerance. Diabetes 61 (2):447-453. doi:10.2337/db11-0995

25. Mari A, Pacini G, Murphy E, Ludvik B, Nolan JJ (2001) A model-based method for assessing insulin sensitivity from the oral glucose tolerance test. Diabetes care 24 (3):539-548

26. Lapolla A, Dalfra MG, Mello G, Parretti E, Cioni R, Marzari C, Masin M, Ognibene A, Messeri G, Fedele D, Mari A, Pacini G (2008) Early detection of insulin sensitivity and beta-cell function with simple tests indicates future derangements in late pregnancy. J Clin Endocrinol Metab 93 (3):876-880. doi:10.1210/jc.2007-1363

27. Hsu WC, Boyko EJ, Fujimoto WY, Kanaya A, Karmally W, Karter A, King GL, Look M, Maskarinec G, Misra R, Tavake-Pasi F, Arakaki R (2012) Pathophysiologic differences among Asians, native Hawaiians, and other Pacific Islanders and treatment implications. Diabetes care 35 (5):1189-1198. doi:10.2337/dc12-0212

28. WHO Expert Consultation (2004) Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 363 (9403):157-163. doi:10.1016/S0140-6736(03)15268-3

29. International Diabetes Federation The IDF consensus worldwide definition of the metabolic syndrome [Internet]. http://www.idf.org/webdata/docs/MetS_def_update2006.pdf. Accessed April 17 2013

30. IADPSG, Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva A, Hod M, Kitzmiler JL, Lowe LP, McIntyre HD, Oats JJ, Omori Y, Schmidt MI (2010) International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes care 33 (3):676-682. doi:10.2337/dc09-1848

31. Savona-Ventura C, Vassallo J, Marre M, Karamanos BG, Group MGS (2012) Hyperglycaemia in pregnancy in Mediterranean women. Acta diabetologica 49 (6):473-480. doi:10.1007/s00592-012-0427-9

Table 1 Descriptive data and results of the main outcome measures for controls and women after GDM, grouped according to glucose tolerance

	Controls	Women after GDM (*n*=470)											
	(*n*=133)	NGT (*n*=280)	*p*	p^b	IFG (*n*=54)	*p*	p^b	IGT (*n*=105)	*p*	p^b	Diabetes (*n*=31)	*p*	p^b
Age (years)	32 (31-33)	33 (32-34)	0.28		36 (33-37)	0.002		35 (34-36)	0.001		36 (32-39)	0.008	
BMI (kg/m^2)	24.0 (23.0-25.4)	23.0 (22.7-23.7)	0.030		24.8 (24.0-27.0)	0.09		25.4 (24.5-26.9)	0.033		31.7 (28.8-35.4)	$2{\cdot}10^{-6}$	
Non-European ethnicity	10 (7)	39 (14)	0.072		10 (19)	0.039		29 (28)	$4{\cdot}10^{-5}$		16 (52)	$4{\cdot}10^{-8}$	
First-degree diabetes heredity	18 (14)	76 (27)	0.001		25 (46)	$5{\cdot}10^{-6}$		42 (40)	$4{\cdot}10^{-6}$		13 (42)	$2{\cdot}10^{-4}$	
Deliveries >3	4 (3)	11 (4)	0.78		6 (11)	0.066		14 (13)	0.006		4 (13)	0.041	
Time to follow-up (days)	419 (410-436)	460 (438-483)	0.16		484 (429-523)	0.11		512 (481-551)	$2{\cdot}10^{-5}$		525 (403-628)	0.064	
HOMA-IR[a]	1.3 (1.1-1.5)	1.4 (1.2-1.5)	0.77	0.84	1.9 (1.6-2.2)	0.021	0.029	1.6 (1.3-1.8)	0.11	0.55	3.2 (2.3-4.4)	$2{\cdot}10^{-5}$	0.010
No. samples available	101 (76)	200 (71)	0.35		38 (70)	0.46		72 (69)	0.24		25 (81)	0.65	
Insulinogenic index[a]	16.6 (14.1-19.6)	13.9 (12.7-15.3)	0.035	0.029	12.8 (9.9-16.6)	0.39	0.30	11.4 (9.9-13.2)	0.003	0.001	7.3 (5.5-9.9)	0.013	0.003
No. samples available	88 (66)	191 (68)	0.74		33 (61)	0.61		69 (66)	1.0		21 (68)	1.0	
Disposition index[a]	13.2 (11.1-15.7)	10.2 (9.3-11.3)	0.010	0.007	6.9 (5.0-9.3)	0.013	0.022	7.8 (6.5-9.4)	$3{\cdot}10^{-4}$	0.002	2.5 (1.8-3.6)	$3{\cdot}10^{-8}$	$1{\cdot}10^{-5}$
No. samples available	86 (65)	187 (67)	0.74		33 (61)	0.74		65 (62)	0.69		21 (68)	0.84	

Data given are the median (95% CI) or *n* (%). All comparisons were performed vs. controls.

Differences in medians were tested with the Mann-Whitney U-test. Frequency differences were tested using Fisher's Exact test.

[a] Log-transformed in main analysis. Values are geometric means (95% CI). Differences were tested by ANOVA adjusting for age, non-European ethnicity, first-degree diabetes heredity, number of deliveries, and time from delivery to follow-up.

[b] When also adjusting for BMI.

GDM, gestational diabetes mellitus; HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance

Table 2 Results of main analysis of the OGTT for women after GDM grouped according to ethnicity

	European (n=362)	Non-European (n=94)	p	p^b	Arab (n=41)	p	p^b	Asian (n=43)	p	p^b
Age (years)	34 (33-34)	35 (33-36)	0.23		35 (31-38)	0.40		35 (32-37)	0.54	
BMI (kg/m^2)	23.8 (23.0-24.0)	25.7 (24.5-27.7)	$9{\cdot}10^{-5}$		28.0 (25.7-32.2)	$2{\cdot}10^{-7}$		24.2 (23.4-25.5)	0.39	
Time to follow-up (days)	462 (442-483)	538 (504-563)	$9{\cdot}10^{-5}$		545 (504-685)	$5{\cdot}10^{-5}$		506 (460-568)	0.11	
HOMA-IR[a]	1.5 (1.3-1.6)	2.0 (1.7-2.3)	0.001	0.033	2.1 (1.6-2.7)	0.004	0.65	1.9 (1.5-2.3)	0.046	0.016
No. samples available	255 (70)	69 (73)	0.61		28 (68)	0.86		32 (74)	0.72	
Insulinogenic index[a]	12.6 (11.6-13.7)	12.7 (10.8-15.1)	0.79	0.91	14.0 (10.8-18.1)	0.32	0.61	12.7 (9.7-16.5)	0.91	0.90
No. samples available	240 (66)	63 (67)	1.0		27 (66)	1.0		29 (67)	1.0	
Disposition index[a]	8.8 (7.9-9.7)	6.8 (5.5-8.4)	0.027	0.26	7.3 (5.3-10.0)	0.24	0.58	6.9 (5.1-9.4)	0.14	0.10
No. samples available	235 (65)	60 (64)	0.9		25 (61)	0.61		29 (67)	0.87	

Data given are the median (95% CI) or *n* (%). All comparisons were performed vs. Europeans. Arab and Asian women are included in the non-European group. Differences in medians were tested with the Mann-Whitney U-test. Frequency differences were tested using Fisher's Exact test.

[a] Log-transformed in main analysis. Values are geometric means (95% CI). Differences were tested by ANOVA adjusting for age and time from delivery to follow-up.

[b] When also adjusting for BMI.

GDM, gestational diabetes mellitus; HOMA-IR, Homeostasis model assessment of insulin resistance

Table 3 Results of logistic regression analyses of variables tested for associations with diabetes after GDM

	Univariate		Multivariate					
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age (years)	1.1 (1.0-1.2)	0.032	1.0 (0.9-1.2)	0.42	1.1 (0.9-1.2)	0.18	1.0 (0.9-1.2)	0.71
BMI (kg/m^2)	1.2 (1.1-1.3)	$7 \cdot 10^{-8}$	1.2 (1.1-1.2)	$5 \cdot 10^{-5}$	1.1 (1.0-1.2)	0.004	1.1 (1.1-1.2)	0.002
Deliveries >3	3.4 (1.0-11.5)	0.053	3.1 (0.7-15)	0.14	4.0 (0.7-24)	0.12	2.0 (0.3-14)	0.44
First-degree diabetes heredity	2.2 (1.0-4.9)	0.053	1.2 (0.4-3.2)	0.71	1.2 (0.4-3.9)	0.72	1.5 (0.4-4.8)	0.27
Non-European ethnicity	6.8 (3.0-15)	$4 \cdot 10^{-6}$	5.0 (1.8-14)	0.002				
Arab ethnicity	10 (3.4-31)	$4 \cdot 10^{-5}$			3.7 (0.9-15)	0.061		
Asian ethnicity	5.0 (1.7-15)	0.004					5.6 (1.5-21)	0.012

All variables were adjusted for time from delivery to follow-up. European ethnicity was used as reference.
Multivariate analyses were performed separately for each ethnic group.
CI, confidence interval; GDM, gestational diabetes mellitus; OR, odds ratio