Epidemiology of Gestational Diabetes Mellitus according to IADPSG/WHO 2013 criteria among Obese Pregnant Women in Europe

AM Egan[1], A Vellinga[1], J. Harreiter [2], D. Simmons[3], G. Desoye [4], R. Corcoy [5,6], J.M. Adelantado [5], R. Devlieger [7], A. van Assche [7], S. Galjaard [7], P. Damm [8], E.R. Mathiesen [8], D.M. Jensen [9], L.L. Andersen [9], A. Lapolla [10], M. Dalfra [10], A Bertolotto [11], U. Mantaj [12],E. Wender-Ozegowska [12], A. Zawiejska [12], D. Hill [13], J.G. Jelsma [14], F.J. Snoek [15], C. Worda [16], D. Bancher-Todesca [16], M.N.M. van Poppel [14], A. Kautzky-Willer [2] FP. Dunne[1] on behalf of the DALI Core Investigator group.

[1] National University of Ireland, Galway, Ireland.

[2] Gender Medicine Unit, Division of Endocrinology and Metabolism, Department of Medicine III, Medical University of Vienna, Vienna, Austria.

[3] Institute of Metabolic Science, Addenbrookes Hospital, Cambridge, England and Macarthur Clinical School, Western Sydney University, Sydney, Australia.

[4] Department of Obstetrics and Gynecology, Medizinische Universitaet Graz, Graz, Austria.

[5] Institut de Recerca de l´Hospital de la Santa Creu i Sant Pau, Barcelona, Spain. [6] CIBER Bioengineering, Biomaterials and Nanotechnology, Instituto de Salud Carlos III, Zaragoza, Spain.

[7] KU Leuven Department of Development and Regeneration: Pregnancy, Fetus and Neonate. Gynaecology and Obstetrics, University Hospitals Leuven, Belgium.

[8] Center for Pregnant Women with Diabetes, Departments of Endocrinology and Obstetrics, Rigshospitalet, Institute of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

[9] Department of Endocrinology and Department of Gynaecology and Obstetrics, Odense University Hospital, Department of Clinical Research, Faculty of Health Science, University of Southern Denmark, Odense, Denmark.

[10] Universita Degli Studi di Padova, Padua, Italy.

[11] Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy.

[12] Medical Faculty I, Poznan University of Medical Sciences, Poznan, Poland

[13] Recherche en Santé Lawson SA, St. Gallen, Switzerland.

[14] Department of Public and Occupational Health, EMGO^{+}-Institute for Health and Care Research, VU University Medical Centre, Amsterdam, the Netherlands.

[15] Department of Medical Psychology, EMGO+-Institute for Health and Care Research, VU University Medical Centre and Medical Psychology AMC, Amsterdam, the Netherlands.

[16] Division of Obstetrics and Feto-Maternal Medicine, Department of Obstetrics and Gynecology, Medical University of Vienna, Vienna, Austria.

Correspondence to:

Prof Fidelma Dunne, Galway Diabetes Research Centre, College of Medicine, Nursing and Health Sciences, National University of Ireland, Galway

Tel: 00-353-91-542039

Fax: 00-353-91-542107

Email: fidelma.dunne@nuigalway.ie

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Abstract

Aims

Accurate prevalence estimates for gestational diabetes mellitus (GDM) amongst pregnant women in Europe are lacking due to the use of a multitude of diagnostic criteria and screening strategies in both high-risk women and the general pregnant population. Our aims were to calculate the prevalence of GDM in early, mid and late gestation in a cohort of women with BMI ≥29 kg/m^2 across 11 centers in Europe using the IADPSG/WHO 2013 diagnostic criteria and to report pregnancy outcomes and important risk factors for GDM.

Methods:

Pregnant women (n=1023, 86.3% European ethnicity) with a body mass index (BMI) ≥29.0kg/m^2 enrolled into the DALI (Vitamin D And Lifestyle Intervention for GDM prevention) pilot, lifestyle and Vitamin D studies of this pan-European multi-center trial, attended for an oral glucose tolerance test (OGTT) in early, mid and late pregnancy. Demographic, anthropometric and metabolic information were obtained at enrolment and throughout pregnancy. GDM was diagnosed using IADPSG/WHO 2013 criteria. GDM treatment followed local policies.

Results:

Numbers recruited per country ranged from 80-217. Dropout (7.1%) was low. Overall, 39% of women developed GDM during pregnancy with no significant differences in prevalence across countries. Prevalence of GDM was high (24%; 242/1023) in early pregnancy. Despite the DALI interventions, a further 14% (94/672) developed GDM when tested at mid gestation (24-28 weeks), and 13% (59/476) of the remaining cohort in late gestation (36 weeks). Demographics and lifestyle factors were similar at baseline between women with GDM and those who maintained normal glucose tolerance (NGT). Previous GDM (16.5% vs 7.9% p=0.002), congenital malformations (6.4% vs 3.3% p=0.045) and macrosomia (31.4% vs 17.9% p=0.001) were reported more frequently in those who developed GDM. Significant anthropometric and

metabolic differences were already present in early pregnancy between women developing GDM or not.

Conclusions:

The prevalence of GDM diagnosed by IADPSG/WHO 2013 GDM criteria in European pregnant women with a BMI ≥29.0 kg/m^2 is substantial, posing a significant health burden to these pregnancies and to the future health of the mother-offspring pair. Criteria for GDM in early pregnancy, supported by robust evidence of the benefits of treatment are urgently needed to guide modern GDM screening and treatment strategies.

Keywords:

Pregnancy

Weight regulation and obesity

Clinical Science and Care

Health care delivery

Clinical diabetes

Epidemiology

Abbreviations

ANOVA	Analysis of Variance
BMI	Body Mass Index
DALI	Vitamin D and Lifestyle Intervention for Gestational Diabetes Mellitus Prevention
EBCOG	European Board and College of Obstetrics and Gynaecology
FIGO	International Federations of Gynecology and Obstetrics
GDM	Gestational Diabetes Mellitus
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes

IADPSG	International Association of the Diabetes and Pregnancy Study Groups
NGT	Normal Glucose Tolerance
OGTT	Oral Glucose Tolerance Test
RCT	Randomised Controlled Trial
WHO	World Health Organisation

Introduction

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy, excluding those with diabetes in pregnancy likely to represent overt diabetes mellitus [1]. Women with GDM are more likely to suffer pregnancy complications and the diagnosis is associated with both immediate and long-term adverse consequences for their offspring [2, 3]. Furthermore, studies investigating postnatal maternal glucose function have shown the prevalence of type 2 diabetes to be as high as 38% in the first year postpartum and as high as 60% in women followed for up to 16 years postpartum [4-6].

The prevalence of GDM in Europe is reported to vary considerably and in certain populations is reported to occur in over 20% pregnancies [7, 8]. Unfortunately, accurate prevalence estimates in Europe are lacking due to highly inconsistent screening and diagnostic criteria both in high-risk women and the general pregnant population [9]. This makes pan-European surveys of GDM very difficult and limits the effects of large scale GDM prevention and treatment strategies. In 2008, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) developed a consensus statement for a new strategy to diagnose GDM [3]. The chosen cut-off points for glucose on a 75-gram glucose tolerance test convey an odds ratio for adverse outcomes of at least 1.75 compared with women with mean glucose levels at 24-28 weeks in the Hyperglycemia and Neonatal Outcomes (HAPO) study [3, 10]. In 2013 both the World Health Organisation (WHO) and the Endocrine Society revised their guidelines and now advise that the IADPSG criteria should be used for the diagnosis of GDM [1, 11]. The International Federation of Gynecology and Obstetrics (FIGO) also support this approach [12]. Recently, the IADPSG has indicated that the criteria are not for use in early pregnancy [13] but have not provided criteria for up to 24 weeks gestation.

The aim of this study was to use information collected during the Vitamin D and Lifestyle Intervention for gestational diabetes mellitus prevention (DALI) trial to determine the

prevalence of GDM in early, mid and late gestation among high risk obese women across 11 centers in Europe using the IADPSG/WHO 2013 diagnostic thresholds. Risk factors and pregnancy outcomes were also evaluated.

Research Design and Methods

The DALI trial was a prospective multi-center, randomised controlled trial (RCT) comparing different lifestyle approaches that may prevent gestational diabetes mellitus (GDM) progression in overweight/obese (BMI ≥29kg/m^2) pregnant women recruited prior to 20 weeks gestation [7, 14, 15]. The presented analysis consists of women from the pilot, lifestyle and Vitamin D cohorts [14,15]. The study enrolled women from 11 centers in 9 European countries representing North, South, East and West areas of Europe [United Kingdom, Ireland, Austria, The Netherlands, Belgium, Denmark (2 sites), Italy (2 sites), Spain, Poland]. Each local research ethics committee approved the study and written informed consent was obtained from all participating subjects. The study was performed in accordance with the principles of the 'Declaration of Helsinki' and registered in ISRCTN registry (ISRCTN70595832). DALI was funded by the European Union 7th framework (FP7/ 2007–2013) under Grant Agreement no.242187.

Patient involvement

Representatives of the target group were interviewed in the developmental stage of the DALI trial about their preferences of intervention content, modality, frequency and location. Patients were not involved in the actual conduct of the study, but participants provided feedback on the burden of the intervention and their experiences with the study in general, as part of a process evaluation. Patient organisations are actively involved in the dissemination of the results to the lay public.

Participants

The main inclusion criteria were: age ≥18 years, singleton pregnancy up to and including 19+6 weeks of gestation, BMI ≥29kg/m^2 before pregnancy, and ability to give informed consent. Exclusion criteria included pre-existing diabetes, the need for complex diets, inability to walk ≥100 meters safely, and significant chronic medical condition or psychiatric disease. Consecutive consenting women undertook a 75g oral glucose tolerance test (OGTT) <20 weeks

gestation, with GDM diagnosed from venous samples using locally available laboratory methods according to the IADPSG/WHO 2013 criteria (fasting plasma glucose ≥ 5.1mmol/L, 1 hour plasma glucose ≥ 10.0 mmol/L and 2 hour plasma glucose ≥ 8.5 mmol/L) (IADPSG). Women diagnosed with GDM at baseline were excluded from the RCT (Lifestyle and/or Vitamin D). The remaining cohort was re-tested in mid gestation (24-28 weeks), and if GDM was not diagnosed, they were retested again in late gestation (35-37 weeks) with further 75g OGTT using IADPSG/WHO 2013 criteria. Recruitment was conducted between January 2012 and February 2014.

Assessments

Information regarding demographics, anthropometric and metabolic factors was obtained from all women at enrolment through anthropometric and metabolic measurements, and by completion of questionnaires (14). A 75g OGTT was performed with blood samples for glucose and insulin taken fasting and, 60, and 120 minutes after glucose ingestion. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using glucose and insulin values [fasting plasma glucose level (mg/dL) x fasting insulin level (microunit/mL) / 405] [16].

Data Analyses

Data were entered into a bespoke web-based electronic database. Descriptive data analysis was performed for all parameters. Continuous variables were summarized by mean ± standard deviation and categorical variables by counts and percentages. Comparisons between GDM and normal glucose tolerant (NGT) obese women were performed using t-Test and/or analysis of variance (ANOVA) for continuous data and Chi square tests for binary data. For non-normally distributed data, non-parametric tests were used to compare ranks between groups. Multivariate logistic regression models were applied to identify risk factors for GDM diagnosis at any time point adjusting for potential confounders. Variables significant in univariate analysis as well as those previously identified as risk factors in the literature were entered into the multivariate model. To avoid collinearity, highly correlated factors were entered in separate models (for

instance, BMI, weight, neck and waist circumference). The risk factor with the highest odds ratio was retained in these instances. Factors (at baseline) included age, weight, BMI, neck/waist circumference, marital status, education, parity, employment, alcohol consumption, smoking, (family) history of GDM and previous pregnancy risk factors (congenital malformation, macrosomic baby, previous pregnancy loss, PCOS, chronic hypertension). Statistical analysis was performed using SPSS 21.0 (SPSS Inc, Chicago, USA). A two-sided p-value <0.05 was considered statistically significant. No permutations were made for missing data.

Results

DALI enrollment

Enrollment occurred across 11 sites in 9 European countries. A total of 1023 women were enrolled (pilot, lifestyle and vitamin D trials) and 73 (7.1%) women dropped out or were lost to follow up across all sites. Enrollment rates (defined as percentage of eligible women enrolled per site) between countries ranged from 7.8 to 21.2% (average 11%) giving a wide spread across the European populations (Table 1).

Prevalence of GDM

Table 2 outlines the GDM prevalence by period of gestation and country. DALI found a high prevalence of GDM of in early pregnancy (<20 weeks gestation) with 242/1023 (24%) women diagnosed. A total of 5 of these women met the criteria for overt diabetes in pregnancy. Of the 242 women diagnosed in early pregnancy, 190 (78.5%) met the diagnostic criteria based on fasting glucose alone (≥ 5.1mmol/L). Women diagnosed in early pregnancy were not enrolled in the randomised controlled trial. There was a spread of prevalence from a low of 10-11% in the United Kingdom and Ireland to the highest in Denmark at 43%. In total, 672 women were re-tested at mid-gestation (24-26 weeks) and 94 (14%) had developed GDM despite the interventions of the trial. Once again there was a spread of prevalence from a low of 8% in Ireland to a maximum of 21% in Italy. Finally, 476 women previously categorized as NGT (without GDM at the OGTT at 24-26 weeks) completed the final OGTT at 36 weeks gestation of whom 59 (13%) developed GDM despite the diet and lifestyle interventions. There was a spread in prevalence from a low of 9% in Italy to a high of 16% in Belgium. Overall 395 (39%) women fulfilled the IADPSG/WHO 2013 GDM criteria at any point within the trials. The lowest overall total prevalence was in United Kingdom at 24% and the highest prevalence was in Denmark at 52%.

Demographic and lifestyle factors:

Table 3 outlines the demographic and lifestyle factors at baseline of all women enrolled in the randomised controlled trials according to glucose tolerance status (GDM at any time versus NGT). There was no significant difference in ethnicity between those who maintained normal glucose tolerance (NGT) and those that developed GDM during the trial. Over 50% reported attaining a high (university equivalent) education reflective of the university cities where recruitment occurred. Attaining a low level of education was similar in women with NGT and GDM at 12.0% and 12.8% respectively. In total 5.2% of mothers reported consuming alcohol during pregnancy. One third of fathers (33.8%) were active smokers, double the rate reported by mothers (16.2%) with no difference in active smoking between women with NGT and GDM. Nulliparous females accounted for 50.3% of the total cohort.

Maternal GDM Risk Factors:

Maternal GDM risk factors at enrolment are displayed in table 4. There were no differences between women with GDM at any time and those with NGT in history of diabetes in a first-degree relative, polycystic ovary syndrome (PCOS), reported chronic hypertension or reported past history of a previous pregnancy loss. More women with GDM than NGT reported a previous history of GDM (7.9% vs 16.5%, p=0.002), congenital malformations (3.3% vs 6.4%, p=0.045) and a previous macrosomic baby (17.9% vs 31.4%, p=0.001).

Anthropometric/metabolic characteristics pre-pregnancy and at first assessment

Table 5 compares anthropometric and metabolic measurements among women with NGT and those with early and mid/late pregnancy GDM. Significant differences between women with NGT and GDM were observed. Reported pre-pregnancy and enrollment weight and BMI were significantly greater in women with GDM in early pregnancy. Waist circumference was significantly different between those with NGT (107.3cm), those with early GDM (114.4cm) and those with GDM in mid- or late-pregnancy (107.1cm) (p=0.009). Significant differences were also noted between groups in terms of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) with higher measurements observed for those women with

GDM in early pregnancy. As expected, women with GDM in early pregnancy had higher fasting, one hour and two hour glucose levels but levels were also significantly higher in women who went on to develop GDM later compared to women with NGT. HOMA index of insulin resistance at first assessment was significantly higher in those with early (4.5) versus mid- or late-GDM (3.6) and those with NGT had the lowest level (3.0) ($p<0.001$).

Risk of GDM development

Table 6 outlines the results of a multivariate logistic regression analysis to evaluate the odds of GDM development. Independent risk factors for GDM development were nulliparity (OR 1.6), neck circumference at initial visit (OR 1.1) and GDM in a previous pregnancy (OR 2.3) and a previous macrosomic baby (OR 1.7).

Pregnancy outcomes according to glucose tolerance.

Table 7 shows pregnancy outcomes for all women enrolled in the study versus those with a diagnosis of GDM in mid and late pregnancy (as those with early GDM were excluded from enrollment) or NGT: no significant differences were found.

Discussion

We found an overall prevalence of GDM of 39%, using IADPSG/WHO 2013 criteria across early, mid and late gestation among overweight/obese women who were evaluated for inclusion in the DALI trial. Participants were well distributed across 11 European centers, the largest cohort attending two sites in Denmark (21.2%). DALI allows for a meaningful interpretation of the European prevalence of GDM as identical screening was used in 11 centers across 9 European states, using WHO 2013 criteria. A substantial proportion was found in early pregnancy (24%), and the other 15% diagnosed equally across mid and late pregnancy. The prevalence of GDM varied across countries, ranging from 52% in Denmark to 24% in the United Kingdom. These findings are in contrast to prior prevalence data that included women across all BMI categories and reported an overall prevalence of 2-6% with a lower prevalence towards the Northern Atlantic seaboard of Europe compared to the Southern Mediterranean seaboard [8]. This variance is likely to be due to lack of uniformity of screening in the aforementioned study, lower glucose cut-off points of IADPSG/ WHO 2013 criteria compared to other guidelines and the inclusion of only those women with a BMI $\geq 29 kg/m^2$ in the current study.

Within this group of women at high risk for GDM, there was no variation in demographics or lifestyle factors according to glucose tolerance, and certain previously reported risk factors were associated with GDM in the logistic regression (prior GDM, prior macrosomia). However, other well-established risk factors for GDM, such as a diagnosis of PCOS and diabetes in a first-degree relative were not significant: this may be due to the overwhelming risk-effect of obesity. The significant risk of GDM observed among these obese women is of concern given the global rise in obesity and the knowledge that both obesity and GDM are independently associated with adverse maternal-fetal outcomes [10, 17]. Furthermore, 70% of obese women with GDM develop type 2 diabetes within 15 years of delivery, compared with 30% of lean women with GDM [18, 19]. It is evident that effective policies to reduce obesity levels are necessary and this may result in both clinical and economic benefits [20]. Indeed,

an initial step may be to ensure universal BMI screening for women of reproductive age. Then, clinicians may be more likely to assist with weight loss and provide appropriate care to identify and reduce secondary complications of increasing BMI [21, 22].

Among women with a BMI ≥29.0 kg/m^2, women with GDM in early pregnancy had a significantly higher weight and BMI compared to those with NGT and those with GDM in mid/late pregnancy. It is an interesting observation that these differences were limited to women with early GDM, while women with GDM in mid/late pregnancy were not significantly different from those with NGT in terms of weight and BMI. Similar findings were observed for neck circumference and systolic and diastolic blood pressure. This is useful clinical information and could be used in a 'risk score' for early GDM, although we would recommend screening all of these women. The use of neck circumference is a novel measure and may overcome inaccuracies associated with measuring waist circumference [23]. After excluding women with early GDM, women who go on to develop GDM in mid/late pregnancy also have elevated glucose levels at baseline compared to those who continue with NGT. This trend is also evident when examining measures of insulin resistance. While there are limitations to indices such as HOMA-IR such as racial differences in mixed populations, they act as a reasonable surrogate for the gold standard euglycemic-hyperinsulinemic clamp [16, 24]. In this study, women with GDM in early pregnancy demonstrated significantly higher insulin resistance compared to those with GDM in later pregnancy or those with NGT as previously reported [25]. These findings support prior work characterizing women with early-onset GDM as having higher levels of insulin resistance and those with GDM in later pregnancy being more similar to women with NGT [26]. Higher BMIs of the women with early-onset GDM is felt to at least partially explain this phenomenon.

Although screening practices vary, one commonly used approach is to screen the majority of women for GDM at 24-28 weeks gestation with earlier testing reserved for those with risk factors [27]. However, almost one quarter of our cohort was positive in early pregnancy (<20

weeks gestation). While the diagnostic cut off values for GDM in early pregnancy are controversial [9, 13], based on our findings there is some evidence that early screening in obese women may be warranted. As the majority of these women were captured using the fasting glucose alone, there may be a role for using this measure rather completing a full OGTT. Screening is of particular importance in the presence of the additional risk factors noted to be independently associated with GDM development at any stage of the study. On multivariate analysis, a history of GDM in a previous pregnancy was the strongest independent risk factor identified (odds ratio 2.3), followed by a history of a macrosomic baby (odds ratio 1.7). Additional independent risks included nulliparity (odds ratio 1.6) and larger neck circumference on initial evaluation (odds ratio 1.1). Women in this study were diagnosed according to the IADPSG/WHO 2013 criteria (1, 3). While international practices vary, this approach adapted by the DALI study is in keeping with recommendations from the European Board and College of Obstetrics and Gynaecology (EBCOG) and FIGO [9]. Due to a lower fasting glucose cutoff of 5.1mmol/L, use of the IADPSG/WHO 2013 criteria result in an increased prevalence of GDM compared to alternative diagnostic criteria, however their use is supported by data revealing that women with fasting plasma glucose levels of 5.1 – 5.5mmol/L have an increased risk of adverse outcomes [27, 28]. It is hoped that there will be a move towards uniformity in the diagnosis of GDM across Europe in the future. This will stimulate research in the field of GDM and give the opportunity for more women to receive a timely diagnosis and appropriate treatment for GDM. It is clear that the criteria for diagnosing GDM in early pregnancy need urgent resolution and studies to delineate these criteria and quantify any benefits from treatment are urgently required.

Limitations of our findings include the fact that women were recruited and consented to partake in a randomised controlled trial which may have resulted in a selection bias. We do not address the optimal GDM prevention strategy as women received a variety of lifestyle modifications and vitamin D therapy during the trial and these are reviewed in the DALI pilot and lifestyle RCT outcomes papers [14, 15]. If there was an impact of the interventions on

individual women, the prevalence of GDM in mid-late pregnancy may be an under-estimate. On the other hand, as discussed in relation to early pregnancy, use of the IADPSG criteria to diagnose additional cases of GDM in late pregnancy is not validated and the justification for this requires further study. Finally, once diagnosed with GDM, women were managed according to local practice at each site and this could influence birth outcomes. Nevertheless, these women represent a wide spectrum of European countries and data were carefully collected, recorded and analysed to give an accurate overview of the patterns of GDM in this population. This work fills an important gap in the literature and highlights the high prevalence of GDM associated with obesity in a European population.

In conclusion, the overall prevalence of GDM diagnosed by the IADPSG/WHO 2013 GDM criteria in European pregnant women participating in the DALI study is 39% with a significant proportion (24%) diagnosed in early pregnancy. Criteria for GDM in early pregnancy, supported by robust evidence of the benefits of early and late treatment are urgently needed to inform pan-European GDM screening and treatment strategy. Such a high GDM prevalence in early pregnancy, and the difficulty in preventing GDM developing de novo, highlights the critical need for preventative interventions before pregnancy.

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Duality of Interest

The authors declare no conflict of interest.

Contribution Statement

AME drafted the manuscript, AV completed the statistical analysis, FPD was the project supervisor and all authors revised the manuscript critically and approved the final version to be published.

References:

1. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization Guideline. Diabetes Res Clin Pract. 2014;103(3):341-63.
2. O'Sullivan EP, Avalos G, O'Reilly M, Dennedy MC, Gaffney G, Dunne FP, et al. Atlantic DIP: the prevalence and consequences of gestational diabetes in Ireland. Ir Med J. 2012;105(5 Suppl):13-5.
3. 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;33(3):676-82.
4. O'Dea A, Tierney M, McGuire BE, Newell J, Glynn LG, Gibson I, et al. Can the Onset of Type 2 Diabetes Be Delayed by a Group-Based Lifestyle Intervention in Women with Prediabetes following Gestational Diabetes Mellitus (GDM)? Findings from a Randomized Control Mixed Methods Trial. J Diabetes Res. 2015;2015:798460.
5. O'Sullivan JB. Establishing criteria for gestational diabetes. Diabetes Care. 1980;3(3):437-9.
6. Metzger BE, Bybee DE, Freinkel N, Phelps RL, Radvany RM, Vaisrub N. Gestational diabetes mellitus. Correlations between the phenotypic and genotypic characteristics of the mother and abnormal glucose tolerance during the first year postpartum. Diabetes. 1985;34 Suppl 2:111-5.
7. Jelsma JG, van Poppel MN, Galjaard S, Desoye G, Corcoy R, Devlieger R, et al. DALI: Vitamin D and lifestyle intervention for gestational diabetes mellitus (GDM) prevention: an European multicentre, randomised trial - study protocol. BMC Pregnancy Childbirth. 2013;13:142.
8. Buckley BS, Harreiter J, Damm P, Corcoy R, Chico A, Simmons D, et al. Gestational diabetes mellitus in Europe: prevalence, current screening practice and barriers to screening. A review. Diabet Med. 2012;29(7):844-54.
9. Benhalima K, Mathieu C, Damm P, Van Assche A, Devlieger R, Desoye G, et al. A proposal for the use of uniform diagnostic criteria for gestational diabetes in Europe: an opinion paper by the European Board & College of Obstetrics and Gynaecology (EBCOG). Diabetologia. 2015;58(7):1422-9.
10. 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(19):1991-2002.
11. Blumer I, Hadar E, Hadden DR, Jovanovič L, Mestman JH, Murad MH, et al. Diabetes and pregnancy: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2013;98(11):4227-49.
12. Hod M, Kapur A, Sacks DA, Hadar E, Agarwal M, Di Renzo GC, et al. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: A pragmatic guide for diagnosis, management, and care. Int J Gynaecol Obstet. 2015;131 Suppl 3:S173-211.
13. McIntyre HD, Sacks DA, Barbour LA, Feig DS, Catalano PM, Damm P, et al. Issues With the Diagnosis and Classification of Hyperglycemia in Early Pregnancy. Diabetes Care. 2016;39(1):53-4.
14. Simmons D, Jelsma JG, Galjaard S, Devlieger R, van Assche A, Jans G, 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(9):1650-6.
15. Simmons D, Devlieger R, Van Assche A, Jans G, Galjaard S, Corcoy R et al. Effect of physical activity and/or healthy eating on GDM risk: The DALI Lifestyle Study. JCEM. 2016; early release December 2016; doi: 10.1210/jc.2016-3455.
16. Pisprasert V, Ingram KH, Lopez-Davila MF, Munoz AJ, Garvey WT. Limitations in the use of indices using glucose and insulin levels to predict insulin sensitivity: impact of race and gender and superiority of the indices derived from oral glucose tolerance test in African Americans. Diabetes Care. 2013;36(4):845-53.
17. Johansson S, Villamor E, Altman M, Bonamy AK, Granath F, Cnattingius S. Maternal overweight and obesity in early pregnancy and risk of infant mortality: a population based cohort study in Sweden. BMJ. 2014;349:g6572.
18. O'Sullivan JB. Subsequent morbidity among gestational diabetic women. In: Sutherland HW, Stowers JM (Eds). Carbohydrate Metabolism in Pregnancy and the Newborn. Churchill Livingstone: Edinburgh; 1984.
19. Guelinckx I, Devlieger R, Beckers K, Vansant G. Maternal obesity: pregnancy complications, gestational weight gain and nutrition. Obes Rev. 2008;9(2):140-50.
20. Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. Lancet. 2011;378(9793):815-25.
21. Zera C, McGirr S, Oken E. Screening for obesity in reproductive-aged women. Prev Chronic Dis. 2011;8(6):A125.
22. Ricart W, López J, Mozas J, Pericot A, Sancho MA, González N, et al. Body mass index has a greater impact on pregnancy outcomes than gestational hyperglycaemia. Diabetologia. 2005;48(9):1736-42.
23. Sebo P, Beer-Borst S, Haller DM, Bovier PA. Reliability of doctors' anthropometric measurements to detect obesity. Prev Med. 2008;47(4):389-93.
24. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab. 2000;85(7):2402-10.
25. Harreiter J, Simmons D, Desoye G, Corcoy R, Adelantado JM, Devlieger R et al. IADPSG and WHO 2013 GDM criteria identify obese women with marked insulin resistance in early pregnancy. Diabetes Care. 2016;39(7):e90-92.
26. Bozkurt L, Göbl CS, Pfligl L, Leitner K, Bancher-Todesca D, Luger A, et al. Pathophysiological characteristics and effects of obesity in women with early and late manifestation of gestational diabetes diagnosed by the International Association of Diabetes and Pregnancy Study Groups criteria. J Clin Endocrinol Metab. 2015;100(3):1113-20.
27. National Institute for Health and Care Excellence (NICE). Diabetes in pregnancy: management from preconception to the postnatal period. 2015. Available at: https://www.nice.org.uk/guidance/ng3 [date last accessed: 3rd May 2016].
28. Djelmis J, Pavic M, Mulliqi Kotori V, Pavlic Renar I, Ivanisevic M, Oreskovic S. Prevalence of gestational diabetes mellitus according to IADPSG and NICE criteria. Int J Gynaecol Obstet. 2016;135(3):250-254.

Table 1: Enrollment of pregnant women in the DALI lifestyle and vitamin D studies by country

Country	Number enrolled	Percentage of total trial population
Spain	99	9.7%
Austria	110	10.8%
Belgium	101	9.9%
Denmark (2 sites)	217	21.2%
Poland	91	8.9%
Italy (2 sites)	116	11.3%
Ireland	84	8.2%
Netherlands	80	7.8 %
United Kingdom	125	12.2%
TOTAL	1023	100%

Table 2: GDM prevalence according to gestation period and country

Country	Number Enrolled	GDM Early pregnancy N (%)	GDM Mid pregnancy N (%)	GDM Late pregnancy N (%)	GDM Total
Spain	99	25/99 (25%)	10/65 (15%)	6/46 (13%)	41/99 (41%)
Austria	110	22/110 (20%)	12/72 (17%)	6/45 (13%)	40/110 (36%)
Belgium	101	21/101 (21%)	12/75 (16%)	10/61 (16%)	43/101 (43%)
Denmark	217	93/217 (43%)	11/106 (10%)	8/77 (10%)	112/217 (52%)
Poland	91	17/91 (19%)	12/68 (18%)	7/47 (15%)	36/91 (40%)
Italy	116	16/116 (14%)	18/85 (21%)	5/54 (9%)	39/116 (34%)
Ireland	84	9/84 (11%)	5/63 (8%)	7/47 (15%)	21/84 (25%)
Netherlands	80	27/80 (34%)	4/44(9%)	1/18 (5%)	32/81 (41%)
United Kingdom	125	12/125 (10%)	10/94 (11%)	9/74(12%)	31/125 (24%)
TOTAL	1023	242/1023 (24%)	94/672 (14%)	59/476 (13%)	395/1023 (39%)

GDM: gestational diabetes mellitus

Table 3: Demographics/Lifestyle factors of participants at enrollment.

	All Women %	NGT %	GDM[a] %	P value
Ethnicity				
European	86.3%	86.4%	86.2%	ns
Non-European	13.7%	13.6%	13.8%	ns
Education				
High	55.2%	56.9%	52.4%	ns
Medium	32.5%	31.1%	34.3%	ns
Low	12.3%	12.0%	12.8%	ns
Living with a partner	93.4%	93.8%	91.8%	ns
Employment status				
Working	77.0%	77.1%	76.8%	ns
Not Working	14.3%	13.8%	15.0%	ns
Home Duties	8.7%	9.1%	8.2%	ns
Current maternal alcohol	5.2%	6.1%	3.8%	ns
Current maternal smoking	16.2%	16.7%	15.4%	ns
Current paternal smoking	33.8%	34.6%	32.6%	ns
Nulliparous	50.3%	48.7%	52.9%	ns

NGT: normal glucose tolerance. GDM: gestational diabetes mellitus. P-value for comparison of women with NGT versus GDM.

[a]Women who developed GDM at any time during pregnancy.

Table 4: Maternal risk factors for GDM development.

	All Women %	NGT %	GDM[a] %	P-value
Diabetes in a first degree relative	24.6%	23.7%	27.7%	ns
Polycystic ovarian syndrome	10.4%	10.3%	10.7%	ns
Chronic hypertension	13.0%	12.8%	13.7%	ns
Previous GDM	9.8%	7.9%	16.5%	0.002
Previous congenital malformation	4.0%	3.3%	6.4%	0.045
Previous macrosomic baby	21.0%	17.9%	31.4%	0.001
Previous pregnancy loss	11.1%	10.2%	14.1%	ns

GDM: gestational diabetes mellitus.
P-value for comparison of women with NGT versus GDM.
[a]Women who developed GDM at any time during pregnancy.

Table 5: Anthropometric/metabolic factors pre-pregnancy and early pregnancy according to glucose tolerance

	NGT	GDM Early Pregnancy	GDM mid-/late-pregnancy	P value comparison of 3 groups	P value comparison early versus mid-/late pregnancy
Age (years)	31.9(5.4)	32.7 (5.1)	32.0 (5.0)	ns	ns
Height (cm)	165.7 (6.7)	165.5 (6.1)	165.0 (7.4)	ns	ns
Pre-pregnancy weight (kg)	92.8 (13.5)	96.8 (16.1)	91.0 (14.9)	<0.001	<0.001
Pre-pregnancy BMI (kg/m^2)	33.7 (4.2)	35.3 (5.4)	33.4 (4.7)	<0.001	<0.001
Weight at enrollment (kg)	94.8 (13.5)	99.3 (17.1)	93.5 (14.7)	<0.001	<0.001
BMI at enrollment (kg/m^2)	34.5 (4.2)	36.2 (5.6)	34.2 (4.4)	<0.001	<0.001
Waist circumference (cm)	107.3 (10.1)	114.4 (60.9)	107.1 (10.1)	0.009	ns
Neck circumference (cm)	36.3 (2.1)	37.4 (4.9)	36.3 (2.2)	<0.001	0.008
Systolic blood pressure (mmHg)	116.4 (11.1)	118.5 (10.1)	115.9 (10.8)	0.03	0.019
Diastolic blood pressure (mmHg)	72.8 (8.5)	75.1 (8.5)	73.0 (11.8)	0.003	0.036[a]
Heart rate (beats/minute)	79 (10.2)	82 (10.6)	81 (9.3)	0.001	ns
Fasting glucose (mmol/L)	4.5 (0.3)	5.2 (0.5)	4.6 (0.3)	<0.001	<0.001
1 hour glucose (mmol/L)	6.5 (1.4	8.9 (2.0)	7.5 (1.4)	<0.001	<0.001
2 hour glucose (mmol/L)	5.7 (1.1)	7.3 (1.7)	6.2 (1.1)	<0.001	<0.001
HOMA Index	3.0 (2.6)	4.5 (2.7)	3.6 (3.6)	<0.001	0.007

Data expressed as mean (standard deviation). HOMA IR: homeostatic model assessment for insulin resistance. NGT: normal glucose tolerance. GDM: gestational diabetes mellitus

[a] not significant when applying Bonferroni adjustment for multiple comparisons.

Table 6: Logistic regression analysis evaluating risk of GDM (yes/no) at any stage of the study.

	Odds ratio	95% CI		p-value
		lower	upper	
Nulliparous	1.6	1.0	2.5	0.032
Neck circumference at initial evaluation (cm)[a]	1.1	1.0	1.2	0.011
GDM in previous pregnancy	2.3	1.3	4.0	0.004
Previous macrosomic baby	1.7	1.1	2.6	0.014

GDM: gestational diabetes mellitus.

[a]Continuous variable

Table 7: Pregnancy outcomes for women enrolled in the trial according to glucose status[a]

	All Enrolled Women %	NGT %	GDM mid/late pregnancy %	P value %
Caesarean section	36.2%	34.1%	40.2%	ns
Pre-eclampsia	3.1%	2.8%	3.8%	ns
Pregnancy-induced hypertension	12.2%	11.3%	14.2%	ns
Birthweight ≥4 kg	16.4%	15.2%	18.5%	ns
Birthweight <2.5kg	3.9%	3.4%	4.8%	ns
Neonatal intensive care unit admission	9.0%	9.9%	6.6%	ns
Gestational at delivery (weeks)	39.6 (5.9)	39.5 (3.0)	39.8 (9.6)	ns
Birth weight (g)	3468 (578)	3456 (524)	3488 (657)	ns
Birth length (cm)	51.4 (3.5)	51.4 (3.3)	51.4 (3.8)	ns

NGT: normal glucose tolerance. GDM: gestational diabetes mellitus.
P-value for comparison of women with NGT versus GDM.
[a]Women with early GDM were excluded from the study therefore pregnancy outcomes are unavailable.