DOI:
10.1111/dme.12482

Document Version
Peer reviewed version

DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

Prediction of Gestational Diabetes by Clinical Risk and Biomarker Profiles. A study in Obese Pregnant Women from the UK Pregnancies Better Eating and Activity (UPBEAT) Pilot Trial

Journal:	*Diabetes, Obesity and Metabolism*
Manuscript ID:	DOM-13-0519-OP
Manuscript Type:	Original Paper
Date Submitted by the Author:	18-Sep-2013
Complete List of Authors:	MAITLAND, RAHAT; King's College London, Division of Women's Health Seed, Paul; King's College London, Division of Women's Health Briley, Annette; Guy's and St. Thomas' NHS Foundation Trust, Women's Health Homsy, Michele; King's College London, Division of Women's Health Thomas, Stephen; Guy's and St. Thomas' NHS Foundation Trust, Women's Health Pasupathy, Dharmintra; King's College London, Division of Women's Health Robson, Stephen; Newcastle Univeristy, Institute of Cellular Medicine Uterine Cell Signalling Group Nelson, Scott; University of Glasgow, Reproductive and Maternal Medicine Sattar, Naveed; University of Glasgow, Institute of Cardiovascular and Medical Sciences Poston, Lucilla; King's College London, Division of Women's Health
Key Words:	adipose tissue, adipocytes, diabetes complications, glycaemic control, insulin resistance, human adipose tissue

Prediction of Gestational Diabetes by Clinical Risk and Biomarker Profiles. A study in Obese Pregnant Women from the UK Pregnancies Better Eating and Activity (UPBEAT) Pilot Trial

Authors: Rahat A Maitland[1], Paul T Seed[1], Annette L Briley[2], Michele Homsy[1], Stephen Thomas[2], Dharmintra Pasupathy[1], Stephen C Robson[3], Scott M Nelson[4], Naveed Sattar[5*], Lucilla Poston[1*]. On behalf of the UPBEAT trial consortium.

Institutions:

[1]Division of Women's Health, Women's Health Academic Centre, King's College London and King's Health Partners, St. Thomas' Hospital, London SE1 7EH, UK

[2]Guy's and St. Thomas' NHS Foundation Trust, London SE1 7EH, UK

[3] Institute of Cellular Medicine, Newcastle University, UK

[4]School of Medicine, University of Glasgow, UK

[5]Institute of Cardiovascular & Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK

[*] Joint senior authors

Corresponding Author:

Dr Rahat A Maitland. Division of Women's Health, Women's Health Academic Centre, King's Health Partners, St. Thomas Hospital, London SE1 7EH, UK

Fax: +44 (0) 20 7620 1227 Telephone: +44 (0) 7974940221

Email: rahat.maitland@kcl.ac.uk

Word count abstract: 249

Word count main text: 2663

Abstract

Aims

Maternal obesity is associated with heightened risk of gestational diabetes (GDM). This study has addressed the prediction of GDM in obese women by routine clinical measures and measurement of biomarkers related to insulin resistance in the early second trimester.

Methods

117 obese pregnant women participating in a pilot trial of a complex intervention of dietary advice and physical activity were studied. Blood samples were obtained at recruitment (15^{+0}-17^{+6}) weeks and demographic, clinical history and anthropometric measures recorded. Biomarkers analysed were plasma lipids (HDL-c, LDL-c, triglycerides), high-sensitivity C-reactive protein [hs-CRP], alanine transaminase [ALT], aspartate transaminase [AST], ferritin, fructosamine, insulin, adiponectin, tissue plasminogen activator [t-PA], interleukin-6 [IL-6], visfatin and leptin). Univariate followed by logistic regression analyses was performed to determine independent predictors and area under the receiver-operating curve (AUC-ROC) calculated for the model.

Results

Of the 106 women included in the analysis, 29 (27.4%) developed GDM. Women with GDM were older, more often of parity ≥2, had higher systolic and diastolic blood pressure, and were more likely to be black (all $p<0.05$). Amongst the blood biomarkers measured, plasma adiponectin alone remained independently associated with GDM in adjusted models ($p=0.002$).

The AUC-ROC for clinical factors alone (0.760) increased significantly (AUC 0.834, $Ch^2(1)$ =4.00, p=0.046) with the addition of adiponectin.

Conclusions

A combination of routinely measured clinical factors and adiponectin measured in the early second trimester in obese women may provide a useful approach to the prediction of GDM. Validation in a large prospective study is required to determine usefulness in clinical practice.

Clinical Trial Reference: ISRCTN89971375

Keywords: gestational diabetes, prediction, adipokines, adiponectin, obesity, pregnancy

Abbreviations: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gestational diabetes (GDM), high sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6), International Association of Diabetes Pregnancy Study Groups (IADPSG), tissue plasminogen activator (t-PA), Body Mass Index (BMI).

Introduction

The prevalence of obesity in adults and children continues to rise. Obesity remains the sixth most important determinant of adverse health and reduced adult life expectancy globally [1]. In the UK, the incidence of obesity in women of reproductive age has almost doubled in the past twenty years [2]; the most recent WHO Global Infobase of obesity (BMI ≥30kg/m^2) in UK females aged more than 15 years (2010) reports an age adjusted prevalence of obesity of 26.3% across all ethnic groups [3].

Maternal obesity carries significant risk of adverse pregnancy outcome, particularly gestational diabetes (GDM). Short and long term metabolic complications follow a continuous linear relationship with BMI [4, 5] with the risk of developing gestational diabetes (GDM) rising from two to eightfold across increasing BMI category [6]. Not all obese women develop GDM, however this heterogeneity poses a burden on limited resources with all women with a BMI >30Kg/m^2 currently managed as if at risk, often resulting in sub-optimal management. Accurate and early identification of pregnant obese women who will subsequently develop GDM women would enable early risk stratification, more appropriate use of health care resources and targeting of intervention strategies.

Currently, the UK National Institute for Health and Clinical Excellence (NICE) recommend selected rather than universal GDM screening, according to risk factors which include obesity. Women with who have previously delivered a macrosomic infant, have had previous GDM, or who have a first degree

relative with diabetes and high risk ethnicity are also screened. This approach yields 60% detection of GDM with a 40% false positive rate in all women [7]. Whilst there is at present no accepted early pregnancy intervention to improve clinical outcome in obese pregnant women [8-10], increased recognition of the problem [11] has led to an international research effort to develop effective interventions. Several large–scale, randomised control trials (RCTs), including the UK Better Eating and Activity Trial (UPBEAT; ISRCTN89971375), are investigating targeted dietary and lifestyle interventions or pharmacological approaches to improve pregnancy outcome in overweight and obese women [12-14].

Research into the prediction of adverse outcomes in other pregnancy related conditions such as pre-eclampsia has shown that a combination of clinical history and early pregnancy clinical measures, together with addition of biomarkers measured in biological samples may provide an effective strategy in early pregnancy risk assessment [15]. Several studies have adopted this approach in prediction of GDM [16, 17], but to our knowledge, not previously in a population of obese women.

In addition to routine demographical data and clinical measurements recorded in early pregnancy in obese women, we have measured biomarkers implicated in the pathogenesis and prediction of type 2 diabetes which reflect inflammatory pathways, markers of adipose tissue function and hepatic fat accumulation and measures of vascular dysfunction [18-21]. These were

evaluated at recruitment in women participating in a pilot trial for the UPBEAT study.

Methods

UPBEAT is a multi-center RCT of a complex dietary and physical activity intervention aimed at improving glucose homeostasis in obese pregnant women (current controlled trials register: ISRCTN89971375). A pilot trial was undertaken in 183 women in four UK hospitals to evaluate changes in dietary and physical activity behaviours, trial all aspects of the protocol and to undertake process evaluation. Details of the intervention and protocol are available on the trial web site (http://www.medscinet.net/upbeat/about.aspx).

Ethical Approval: NHS Research Ethics Committee approval was obtained in all contributing centres (UK IRAS integrated research application system; reference 09/H0802/5).

At recruitment (15^{+0}-17^{+6} weeks gestation) and following informed consent, information was obtained on demography, maternal history, maternal family and current pregnancy health. One week later, women were randomised to the intervention arm or control arm, which consists of standard antenatal care. Blood pressure was recorded using the Microlife® BP3BT0-A automated blood pressure monitor which is validated for use in pregnancy. Maternal skinfold thickness (triceps, biceps, subscapular and supra-iliac) were measured in triplicate with Harpenden skinfold calipers (validated for values ≤80mm) (Holtain Ltd, Wales, UK) in addition to the following circumferences: waist, mid

arm, thigh and hip. Total sum of skinfolds was calculated at four sites (triceps, biceps, suprailiac and subscapular). Blood samples were obtained from 117 women in the three centres that had facilities for sample handling and storage. Serum and plasma was stored at -80°C for future analysis.

At 28 weeks' gestation an oral glucose tolerance test was performed on all women. Diagnosis of GDM following a 75g 2-h OGTT at 27^{+0}-28^{+6} weeks' was defined according to the International Association of Diabetes Pregnancy Study Groups (IADPSG) criteria (fasting blood glucose ≥5.1mmol/l or 1-hr glucose ≥10.0mmol/l or 2-hr glucose ≥8.5mmol/l)[22]. If a diagnosis of GDM was made, women were referred for routine GDM care according to local criteria.

Biochemical analyses: plasma total cholesterol, HDL-cholesterol triglycerides, ALT, AST, hs-CRP, fructosamine (c311, Roche Diagnostics, Burgess Hill, UK) and ferritin (elecsys 2010, Roche Diagnostics, Burgess Hill, UK) were measured on clinically validated automated platforms using the manufacturers' quality controls and calibration materials. Coefficients of variation (CVs) were <6%. Plasma insulin was measured with an enzyme linked immunosorbent assay (ELISA) (Mercodia, Uppsala, Sweden) that does not cross-react with proinsulin and the interassay CV was <7%. Baseline plasma adiponectin, IL-6, leptin (R&D Systems, Abingdon, U.K.) t-PA (Stago, Theale, UK) and visfatin (Phoenix peptide, Karlsruhe, Germany) were measured by enzyme-linked immunosorbent assay. These methods had inter-assay CV's <10%.

All analyses were performed on previously unthawed EDTA and serum samples. Samples were processed by technicians blinded to the identity of the samples.

Statistical methods

The analysis was essentially exploratory with the aim of identifying potentially useful combinations of clinical and biochemical predictors of maternal GDM. Standard distributional checks (BoxCox regression and Normal distribution plots) were carried out, and separate decisions made on the appropriate transformation. Based on these findings, log transformation was made for all biochemical variables. Differences between patient groups are reported as geometric means and ratios of geometric means, with 95% confidence intervals.

The association of clinical indicators with GDM was established using linear or logistic regression as appropriate, with robust standard errors. Biochemical indicators were assessed as predictors of GDM, adjusting for significant clinical indicators.

The overall performance of the markers as predictors of GDM was assessed by comparison of ROC areas. Where necessary, composite predictors were derived using multiple logistic regression.

All data analysis was carried out in the statistical package Stata, version 11.2 (StataCorp, College Station, Texas).

Results

11 women were omitted from analysis because of inadequate OGTT data. Of the remaining 106, 29 were diagnosed with GDM (27.4%). Demographic and clinical characteristics of women who developed GDM compared to those who did not are summarised in Table 1. In general, women with GDM were older, more often of higher parity (≥2), had increased systolic and diastolic blood pressure and were more likely to be black. BMI was not significantly different between the two groups, although skinfold thicknesses were greater in women who developed GDM; women who developed GDM had greater triceps (37.40mm v 31.36mm p=0.004) and total sum of skinfolds thickness (93.88mm v 86.06mm p=0.031). There was no evidence of interaction in terms of prediction of GDM by treatment group (p=0.85).

Table 2 summarises the first trimester biomarkers for women who subsequently developed develop GDM and those who did not. Women with GDM had 34% lower plasma concentrations of adiponectin [95% CI -47% to -19%], adjusting for clinical predictors: age, parity ≥2, DBP and SBP. There was a trend towards significance for fructosamine in the GDM group (p=0.05), which attenuated to the null following adjustment (p=0.82). No other biochemical markers were associated with GDM (Table 2).

In a combined logistic regression model including the biomarkers and clinical risk factors, the only consistent predictive variables were adiponectin (OR for a halving in adiponectin concentration 4.04 [95% CI 1.69 to 9.64], p= 0.002)

and maternal age (OR per additional year 1.179, [95% CI 1.04 to 1.337], p=0.01) (Table 3).

An AUC-ROC of 0.760 [95% CI 0.645 to 0.875] for prediction of GDM was achieved with clinical predictors (age, parity, ethnicity and blood pressure) alone. The AUC-ROC increased significantly to 0.834 [95% CI 0.742 to 0.927] ($Ch^2(1)=4.00$, p=0.046) with addition of adiponectin (Figure 1).

Further sensitivity analysis was conducted with addition of maternal anthropometry increasing the AUC-ROC for clinical predictors alone to 0.796 [95% CI 0.692 to 0.898] (supplement Table 1) however in the fully adjusted model, only a low concentration of adiponectin remained independently predictive of GDM.

Discussion

This study highlights novel biochemical and clinical factors for the prediction of GDM in obese pregnant women and suggests that an algorithm based on simple clinical variables plus adiponectin may provide a clinically useful method for prediction of GDM in this population.

Four previous studies have identified a number of patient characteristics and biomarkers associated with the prediction of GDM [16, 23-25]. These have been undertaken in populations of mixed risk, including non-caucasian ethnicity [16, 23, 25], a family history of diabetes [16, 23-25], previous history of GDM [16, 23, 25], increased pre-pregnancy BMI [16, 24, 25], increased

maternal age [16, 23, 25] and of differing parity [24]. Savvidou et al measured nine biomarkers in the first trimester and found that high tPA and low HDL increased the AUC-ROC from 0.824 with clinical risk factors alone to 0.861 in a group of all comers regardless of baseline BMI [24]. The addition of adiponectin to prediction models for GDM has consistently increased the AUC-ROC to values above those achieved with clinical measures alone. Further inclusion of adipokines and biomarkers has frequently demonstrated a modest, non-significant increase in the AUC-ROC. For example, in a case controlled study of 400 women, those with GDM were reported to have increased maternal serum visfatin and decreased serum adiponectin concentrations at 11-13 weeks. The addition of adiponectin to the prediction model using clinical measures alone resulted in a significant change in the AUC-ROC whereas there was a non-significant increase following addition of visfatin (AUC-ROC 0.828 [maternal characteristics alone], 0.854 [adiponectin] and 0.855 [adiponectin and visfatin]) [16]. Nanda et al measured three biomarkers and found that in the GDM group, compared to controls, adiponectin and sex hormone-binding globulin (SBGH) were lower. When screening for GDM by maternal characteristics alone, the detection rate was 61.6% (false-positive rate of 20%) increasing to 74.1% with the addition of adiponectin and SHBG [25]. Alternative approaches to GDM risk assessment have included measurement of biomarkers in the preconception period, a recent report finding that maternal characteristics, fasting plasma glucose, glycosuria and preconception dyslipidaemia yielded an AUC-ROC of 0.90 for the prediction of GDM [23]. However, the varied diagnostic criteria for GDM used in previous studies has limited comparisons between previous attempts

to predict GDM. Importantly, none has specifically addressed risk assessment in obese pregnant women, which has important implications for clinical practice given the recognition of obesity as the major risk factor for GDM, and the likelihood that the biomarker profile may be dissimilar from other risk groups in women with a high BMI.

Our results suggest that clinically useful prediction of GDM in obese pregnant women is achievable using a combination of clinical characteristics (older age, increased blood pressure [SBP and DBP], parity ≥2 and black ethnicity) combined with the plasma concentration of adiponectin. To reflect current clinical practice, routine clinical measurements recorded at antenatal visits were included. The inclusion of detailed maternal anthropometry (including skin-fold thicknesses), which is undertaken in all women participating in the UPBEAT trial suggested a limited potential role for taking such measurements routinely as an aid to GDM prediction (supplement Figure 1).

Adiponectin, an adipocyte derived adipokine, is now recognised as being strongly associated with improved glucose metabolism and increasing insulin sensitivity, although the causality of this relationship remains debated. Irrespective of causal direction, adiponectin appears to provide a good 'read-out' of whole body insulin sensitivity. In a recent meta-analysis of non-pregnant individuals adiponectin was shown to be strongly predictive of type 2 diabetes, and inversely related to measures of insulin resistance and BMI [18].

The role of adiponectin in obese pregnant women may extend beyond usefulness as a biomarker. In the Hyperglycemia and Adverse Pregnancy Outcome (HAPO), serum concentrations of adiponectin declined as glucose and maternal BMI increased and adiponectin was inversely associated with birth weight, neonatal skin fold thickness and total body fat (estimated using anthropometry), giving rise to the hypothesis that this cytokine may play a role in fetal growth regulation by modulation of placental nutrient transport in addition to maternal glucose homeostasis [26]. Data in support of a placental origin of adiponectin remains equivocal, with evidence favouring maternal origin of adiponectin measured in the blood of pregnant women [27]. Maternal adiponectin has, therefore, the potential to be a 'functional' target for interventions in obese pregnant women whereby achievement of increased plasma concentrations could parallel a reduced risk of macrosomia. This may be a realistic target as adiponectin has been shown to be modifiable by dietary intervention in non-pregnant populations [28, 29]. Lifestyle interventions in pregnant women of differing pre-pregnancy BMI categories have been equivocal in regard to effects on glucose metabolism and insulin resistance although none has measured adiponectin [30-32]. Following completion of the UPBEAT (1546 women), the influence of the intervention on plasma adiponectin concentration will therefore be explored.

To the best of our knowledge there have been no previous studies of adiponectin and GDM in an exclusively obese population but the findings are consistent with other reports in women of all BMI categories with established disease or prior to the development of GDM [25, 33, 34]. A recent case

controlled study from Brazil of 79 and 129 women of mixed ethnicity with and without GDM respectively, reported that GDM was associated with significantly lower serum concentrations of adiponectin in the third trimester (28-36 weeks) compared to controls (p=0.0015). GDM and BMI both had an independent association with adiponectin with no significant interaction between the two factors (GDM: p = 0.04, BMI: p= 0.01 and interaction: p = 0.76 following a two-way ANOVA test) [35]. In contrast, although adiponectin was significantly lower in women who developed GDM in our previous study in women of mixed risk [24], it did not contribute to the final model which combined two factors (HDL-c and t-PA antigen), both recognised to be related to adiponectin via linked hepatic / circulating triglyceride-mediated pathways [36] .

Low serum adiponectin concentrations appear to be associated with ethnic groups known to have a higher risk of developing incident type 2 diabetes later in life [37]. In the present study, women of black ethnic origin had significantly lower plasma levels of adiponectin than non-black women, and a previous report has shown lower adiponectin concentrations in pregnant women of South Asian origin [33].

We also observed that adiponectin was significantly related to current smoking status, a finding previously reported in a non-pregnant population in which the plasma adiponectin concentration increased in a stepwise fashion with never, past and current smokers [38, 39].

There were limitations to our study. The sample size was small and the data obtained should be considered as a training set for later validation in the UPBEAT trial. Furthermore, fasting blood samples were not obtained at randomisation (15^{+0}-17^{+6}), precluding the measurement of the fasting glucose or insulin concentration. However, as fasting is not mandatory for antenatal clinic visits, this study was designed pragmatically, to be relevant to current clinical practice.

In summary, we have demonstrated that the risk of developing GDM in obese pregnant women may be predicted in the early second trimester of pregnancy by using an algorithm, which incorporates routine clinical variables as well as the biochemical marker adiponectin. Our findings therefore extend prior studies and collectively suggest that by additionally measuring adiponectin in high-risk women before routine clinical diagnosis of GDM, a potential therapeutic window for intervention could be created. Since GDM is associated with increased risk of incident type 2 diabetes and 10 year cardiovascular risk in mothers [40], as well as maternal and neonatal pregnancy complications, successful intervention has the potential to improve both short and long term outcomes. We conclude that further large scale studies of GDM prediction in obese pregnant women are warranted.

Acknowledgments

We thank the UPBEAT study research midwives, health trainers and all the pregnant women who took part. We also thank Dr Paul Welsh, Dr Lynne

Cherry and Elaine Butler (University of Glasgow) for their excellent technical input.

Funding

This paper presents independent research funded by the National Institute for Health Research (NIHR) under the Programme Grants for Applied Research funding stream (Ref: RP-0407-10452). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. The study was also supported by Guy's and St.Thomas' Charity; Reg Charity 251983, UK Chief Scientist Office, Scottish Government Health Directorates, Edinburgh, UK and Tommy's Charity; Reg Charity 1060508, UK.

Duality of interest: The authors declare that there is no duality of interest associated with this manuscript.

Author Contributions

RM researched data and wrote the original manuscript. MH and SN edited the manuscript and contributed to the discussion. ST, DP, SR reviewed the manuscript. AB researched data and is the UPBEAT clinical trial manager. PS performed the statistical analysis and edited the manuscript. LP and NS supervised RM, researched data and edited the manuscript.

References

1. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJL. Selected major risk factors and global and regional burden of disease. The Lancet. 2002;360(9343):1347-1360.
2. Heslehurst N, Rankin J, Wilkinson JR, Summerbell CD. A nationally representative study of maternal obesity in England, UK: trends in incidence and demographic inequalities in 619 323 births, 1989-2007. Int J Obes (Lond). 2010;34(3):420-428.
3. World Health Organisation. WHO Global InfoBase. 2010; Available from: http://infobase.who.int.
4. Sebire NJ, Jolly M, Harris JP, Wadsworth J, Joffe M, Beard RW, et al. Maternal obesity and pregnancy outcome: a study of 287,213 pregnancies in London. Int J Obes Relat Metab Disord. 2001;25(8):1175-1182.
5. Athukorala C, Rumbold A, Willson K, Crowther C. The risk of adverse pregnancy outcomes in women who are overweight or obese. BMC Pregnancy and Childbirth. 2010;10(1):56.
6. Chu SY, Callaghan WM, Kim SY, Schmid CH, Lau J, England LJ, et al. Maternal obesity and risk of gestational diabetes mellitus. Diabetes Care. 2007;30(8):2070-2076.
7. National Institute for Health and Clinical Excellence (NICE). Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period [CG63] 2008; London.
8. Dodd JM, Grivell RM, Crowther CA, Robinson JS. Antenatal interventions for overweight or obese pregnant women: a systematic review of randomised trials. BJOG. 2010;117(11):1316-1326.
9. Oteng-Ntim E, Varma R, Croker H, Poston L, Doyle P. Lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcome: systematic review and meta-analysis. BMC Medicine. 2012;10:47(1).
10. Thangaratinam S, Rogozińska E, Jolly K, Glinkowski S, Roseboom T, Tomlinson JW, et al. Effects of interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence. BMJ. 2012;344.

11. Rasmussen K, Yaktine A. Institute of Medicine (IOM). Weight Gain During Pregnancy: Reexamining the Guidelines. The National Academies Press. 2009.

12. Dodd JM, Turnbull DA, McPhee AJ, Wittert G, Crowther CA, Robinson JS. Limiting weight gain in overweight and obese women during pregnancy to improve health outcomes: the LIMIT randomised controlled trial. BMC Pregnancy Childbirth. 2011;11:79.

13. Walsh J, Mahony R, Foley M, Mc Auliffe F. A randomised control trial of low glycaemic index carbohydrate diet versus no dietary intervention in the prevention of recurrence of macrosomia. BMC Pregnancy Childbirth. 2010;10:16.

14. Nelson SM, Matthews P, Poston L. Maternal metabolism and obesity: modifiable determinants of pregnancy outcome. Hum Reprod Update. 2010;16(3):255-275.

15. Akolekar R, Syngelaki A, Poon L, Wright D, Nicolaides KH. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. Fetal Diagn Ther. 2013;33(1):8-15.

16. Ferreira AFA, Rezende JC, Vaikousi E, Akolekar R, Nicolaides KH. Maternal Serum Visfatin at 11-13 Weeks of Gestation in Gestational Diabetes Mellitus. Clin Chem. 2011;57(4):609-613.

17. Lacroix M, Battista M-C, Doyon M, Ménard J, Ardilouze J-L, Perron P, et al. Lower Adiponectin Levels at First Trimester of Pregnancy Are Associated With Increased Insulin Resistance and Higher Risk of Developing Gestational Diabetes Mellitus. Diabetes Care. 2013;36(6):1577-1583.

18. Li S, Shin HJ, Ding EL, van Dam RM. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2009;302(2):179-188.

19. Fraser A, Harris R, Sattar N, Ebrahim S, Davey Smith G, Lawlor DA. Alanine aminotransferase, gamma-glutamyltransferase, and incident diabetes: the British Women's Heart and Health Study and meta-analysis. Diabetes Care. 2009;32(4):741-750.

20. Wannamethee SG, Sattar N, Rumley A, Whincup PH, Lennon L, Lowe GD. Tissue plasminogen activator, von Willebrand factor, and risk of type 2 diabetes in older men. Diabetes Care. 2008;31(5):995-1000.

21. Lee CC, Adler AI, Sandhu MS, Sharp SJ, Forouhi NG, Erqou S, et al. Association of C-reactive protein with type 2 diabetes: prospective analysis and meta-analysis. Diabetologia. 2009;52(6):1040-1047.

22. International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy. Diabetes Care. 2010;33(3):676-682.

23. Gobl C, Bozkurt L, Rivic P, Schernthaner G, Weitgasser R, Pacini G, et al. A two-step screening algorithm including fasting plasma glucose measurement and a risk estimation model is an accurate strategy for detecting gestational diabetes mellitus. Diabetologia. 2012;55(12):3173-3181.

24. Savvidou M, Nelson SM, Makgoba M, Messow CM, Sattar N, Nicolaides K. First-Trimester Prediction of Gestational Diabetes Mellitus: Examining the Potential of Combining Maternal Characteristics and Laboratory Measures. Diabetes. 2010;59(12):3017-3022.

25. Nanda S, Savvidou M, Syngelaki A, Akolekar R, Nicolaides KH. Prediction of gestational diabetes mellitus by maternal factors and biomarkers at 11 to 13 weeks. Prenat Diagn. 2011;31(2):135-141.

26. Lowe LP, Metzger BE, Lowe WL, Dyer AR, McDade TW, McIntyre HD, et al. Inflammatory Mediators and Glucose in Pregnancy: Results from a Subset of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. J Clin Endocrinol Metab. 2010;95(12):5427-5434.

27. Aye IL, Powell TL, Jansson T. Review: Adiponectin--the missing link between maternal adiposity, placental transport and fetal growth? Placenta. 2013;34 Suppl:S40-45.

28. Yang WS, Lee WJ, Funahashi T, Tanaka S, Matsuzawa Y, Chao CL, et al. Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. J Clin Endocrinol Metab. 2001;86(8):3815-3819.

29. Esposito K, Pontillo A, Di Palo C, Giugliano G, Masella M, Marfella R, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. JAMA. 2003;289(14):1799-1804.

30. Oostdam N, van Poppel M, Wouters M, Eekhoff E, Bekedam D, Kuchenbecker W, et al. No effect of the FitFor2 exercise programme on blood

glucose, insulin sensitivity, and birthweight in pregnant women who were overweight and at risk for gestational diabetes: results of a randomised controlled trial. BJOG. 2012;119:1098-1107.

31. Wolff S, Legarth J, Vangsgaard K, Toubro S, Astrup A. A randomized trial of the effects of dietary counseling on gestational weight gain and glucose metabolism in obese pregnant women. Int J Obes (Lond). 2008;32(3):495-501.

32. Barakat R, Cordero Y, Coteron J, Luaces M, Montejo R. Exercise during pregnancy improves maternal glucose screen at 24-28 weeks: a randomised controlled trial. Br J Sports Med. 2012;46(9):656-661.

33. Retnakaran R, Hanley AJG, Raif N, Connelly PW, Sermer M, Zinman B. Reduced Adiponectin Concentration in Women With Gestational Diabetes. Diabetes Care. 2004;27(3):799-800.

34. Williams MA, Qiu C, Muy-Rivera M, Vadachkoria S, Song T, Luthy DA. Plasma Adiponectin Concentrations in Early Pregnancy and Subsequent Risk of Gestational Diabetes Mellitus. J Clin Endocrinol Metab. 2004;89(5):2306-2311.

35. Gueuvoghlanian-Silva BY, Torloni MR, Mattar R, de Oliveira LS, Scomparini FB, Nakamura MU, et al. Profile of inflammatory mediators in gestational diabetes mellitus: phenotype and genotype. Am J Reprod Immunol. 2012;67(3):241-250.

36. Sattar N, Wannamethee S, Forouhi N. Novel biochemical risk factors for type 2 diabetes: pathogenic insights or prediction possibilities? Diabetologia. 2008;51(6):926-940.

37. Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA, et al. Adiponectin and development of type 2 diabetes in the Pima Indian population. Lancet. 2002;360:57-58.

38. Miyazaki T, Shimada K, Mokuno H, Daida H. Adipocyte derived plasma protein, adiponectin, is associated with smoking status in patients with coronary artery disease. Heart. 2003;89(6):663.

39. Nanda S, Akolekar R, Sodre D, Vaikousi E, Nicolaides KH. Maternal serum adiponectin at 11-13 weeks of gestation in pregnancies delivering small for gestation neonates. Fetal Diagn Ther. 2011;29(4):274-279.

40. Fraser A, Nelson SM, Macdonald-Wallis C, Cherry L, Butler E, Sattar N, et al. Associations of pregnancy complications with calculated cardiovascular disease risk and cardiovascular risk factors in middle age: the Avon Longitudinal Study of Parents and Children. Circulation. 2012;125(11):1367-1380.

Table 1

Simple unadjusted comparisons of clinical predictors by OGTT test result

Maternal Characteristic	GDM (IADPSG) N=29	No GDM N=77	Comparison (95% CI)	P value
Age (years)	33.48 (±4.40)	30.19 (±5.31)	3.29 (1.28 to 5.30)	0.002
Age categories				0.030
18-25	2 (6.9%)	17 (22.1%)	-	-
26-30	4 (13.8%)	20 (26.0%)	1.70 (0.28 to 10.45)	-
31-40	10 (34.5%)	26 (33.8%)	3.27 (0.64 to 16.80)	-
35 plus	13 (44.8%)	14 (18.2%)	7.89 (1.52 to 41.02)	-
Height (m)	1.65 (±0.08)	1.65 (±0.07)	0.00 (-0.03 to 0.03)	0.944
Weight (kg)	95.79 (±12.38)	97.98 (±15.56)	-2.19 (-7.93 to 3.54)	0.450
BMI (kg/m^2)	35.27 (±3.60)	36.11 (±4.95)	-0.84 (-2.57 to 0.89)	0.337
Circumferences (cm)				
Waist	107.83 (±7.42)	107.56 (±10.75)	0.27 (-3.37 to 3.91)	0.884
Mid arm	37.83 (±4.05)	37.21 (±3.98)	0.62 (-1.11 to 2.35)	0.479
Hip	120.48 (±9.23)	122.87 (±11.80)	-2.39 (-6.69 to 1.92)	0.274
Thigh	66.41 (±8.97)	69.36 (±7.69)	-2.95 (-6.66 to 0.76)	0.118
Skinfolds (mm)				
Triceps	37.40 (±10.15)	31.36 (±7.36)	6.04 (1.98 to 10.10)	0.004
Biceps	28.00 (±9.54)	24.42 (±7.50)	3.58 (-0.30 to 7.46)	0.070
Subscapular	35.97 (±8.19)	32.22 (±9.15)	3.74 (0.10 to 7.39)	0.044
Suprailiac	29.91 (±8.28)	29.73 (±8.26)	0.18 (-3.38 to 3.74)	0.920
Total	93.88 (±16.47)	86.06 (±16.65)	7.82 (0.72 to 14.92)	0.031
SBP (mmHg)	123.31 (±7.89)	119.04 (8.68)	4.26 (0.77 to 7.75)	0.017
DBP (mmHg)	76.44 (±7.52)	72.54 (6.65)	3.90 (0.77 to 7.03)	0.015
Ethnicity				
Black	16/29 (±55.2%)	21/77 (±27.3%)	3.28 (1.35 to 7.97)	0.009
Asian	0/29 (±0.0%)	1/77 (±1.3%)	0.00 (0.00 to ∞)	0.991
Other	2/29 (±6.9%)	2/77 (±2.6%)	2.78 (0.37 to 20.70)	0.319

Parity				
0	9 (31%)	37 (48.1%)	-	-
1	10 (34.5%)	31 (40.3%)	1.33 (0.48 to 3.67)	-
2 or more	10 (34.5%)	9 (11.7%)	4.57 (1.43 to 14.55)	-
Previous GDM	1/29 (±3.4%)	1/77 (±1.3%)	2.71 (0.16 to 44.88)	0.485
Smoking				
Never	8/29 (27.6%)	33/77 (42.9%)	0.51 (0.20 to 1.29)	0.154
Current	2/29 (6.9%)	5/77 (6.5%)	1.07 (0.20 to 5.83)	0.941
Number of cigarettes (<8 weeks)				-
0	27 (93.1%)	66 (85.7%)	-	-
1-5 per day	2 (6.9%)	2 (2.6%)	2.44 (0.33 to 18.25)	-
6-10 per day	0 (0.0%)	5 (6.5%)	-	-
11-20 per day	0 (0.0%)	4 (5.2%)	-	-

Table 2

Comparisons of biomarkers by OGTT test result (geometric means & ratios).

(adjusted for routinely used clinical predictors: age, parity (>=2), Black ethnicity, SBP and DBP)

Biomarker*	GDM (IADPSG)	No GDM	Comparison (95% CI)	P value
Fructosamine (umol/l)	n=28 200.87 (1.10)	n=77 192.90 (1.09)	1.00 (0.97 to 1.04)	0.816
ALT (U/L)	n=28 21.41 (1.79)	n=77 19.00 (1.57)	1.12 (0.84 to 1.50)	0.423
AST (U/L)	n=28 30.63 (1.53)	n=77 25.07 (1.41)	1.17 (0.96 to 1.43)	0.109
Ferritin (ng/ml)	n=28 42.06 (2.27)	n=77 39.48 (2.29)	0.95 (0.64 to 1.41)	0.785
Adiponectin (µg/ml)	n=28 4.97 (1.72)	n=77 7.34 (1.76)	0.66 (0.53 to 0.81)	0.000
tPA (ng/ml)	n=28 10.35 (1.49)	n=77 9.00 (1.47)	1.05 (0.86 to 1.28)	0.644
iL-6 (pg/ml)	n=27 1.01 (2.08)	n=75 0.95 (2.54)	0.91 (0.66 to 1.24)	0.547
Leptin (pg/ml)	n=28 53.82 (1.49)	n=74 59.36 (1.52)	0.92 (0.76 to 1.13)	0.438
Visfatin (ng/ml)	n=28 4.94 (1.40)	n=74 5.28 (1.42)	0.93 (0.77 to 1.12)	0.416
Insulin (mU/l)	n=29 26.00 (2.99)	n=77 20.20 (2.78)	1.33 (0.80 to 2.21)	0.270
Cholesterol (mmol/l)	n=29 5.31 (1.18)	n=77 5.42 (1.21)	1.01 (0.93 to 1.10)	0.801
Triglycerides (mmol/l)	n=29 1.67 (1.42)	n=77 1.53 (1.38)	1.13 (0.96 to 1.32)	0.134
HDL (mmol/l)	n=29 1.64 (1.32)	n=77 1.71 (1.26)	0.94 (0.82 to 1.08)	0.391
CRP (mg/l)	n=29 9.18 (1.93)	n=77 7.77 (2.30)	1.28 (0.89 to 1.83)	0.179
VLDL (mmol/l)	n=29 0.76 (1.42)	n=77 0.71 (1.38)	1.13 (0.97 to 1.32)	0.118
LDL (mmol/l)	n=29 2.74 (1.39)	n=77 2.93 (1.34)	0.99 (0.86 to 1.14)	0.862
Cholesterol:HDL	n=29 3.23 (1.31)	n=77 3.17 (1.27)	1.07 (0.95 to 1.21)	0.265
LDL:HDL	n=29 1.67 (1.56)	n=77 1.71 (1.45)	1.05 (0.87 to 1.27)	0.631

*indicates geometric means and ratios of geometric means

Only adiponectin predictive after allowing for major clinical variables.

Table 3

Combined logistic regression using biomarkers and routine clinical risk factors that were significant in tables 1 and 2 (age, parity [>=2], Black ethnicity, SBP, DBP and adiponectin)

	Odds Ratio	Std. Error	z	P>|z|	95% Conf. Interval
Log adiponectin	0.1333	0.853	-3.15	0.002	0.038 to 0.467
Age	1.179	0.076	2.57	0.010	1.040 to 1.337
Parity ≥2	2.091	1.524	1.01	0.312	0.501 to 8.725
Black ethnicity	1.349	0.802	0.50	0.615	0.420 to 4.328
SBP	1.038	0.047	0.83	0.409	0.950 to 1.134
DBP	1.075	0.054	1.45	0.148	0.975 to 1.186

Figure 1

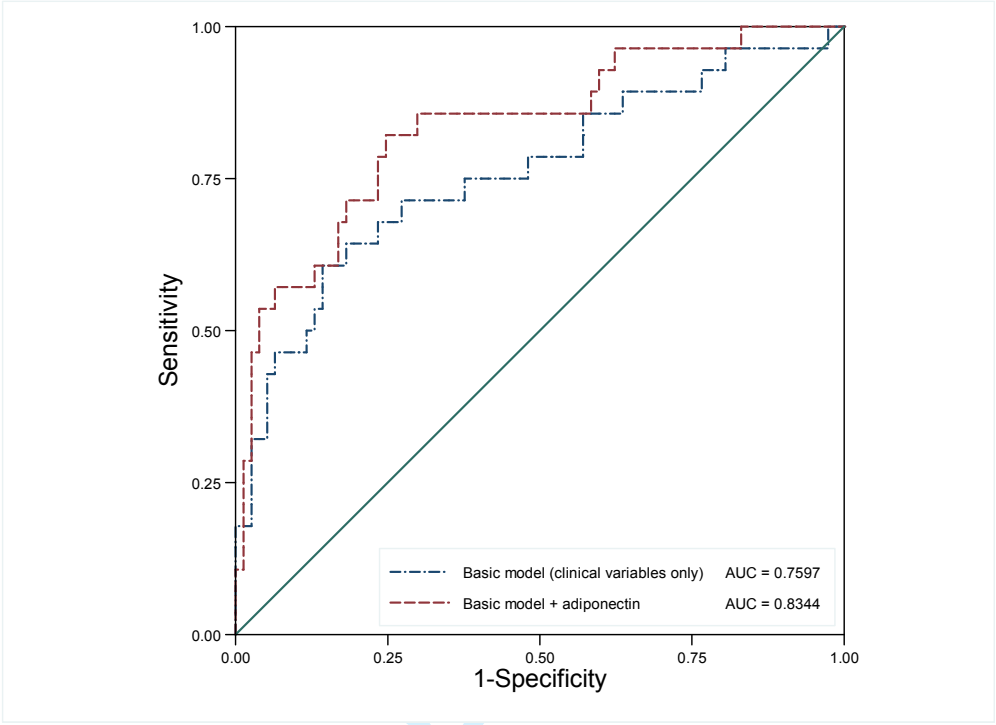

Figure 1: ROC curve and summaries using the basic model (including age, parity, ethnicity, blood pressure), with the addition of adiponectin. AUC, area under ROC curve.

Supplement 1 (Online Appendix File)

Table 1

Combined logistic regression using biomarkers and routine clinical risk factors that were significant in supplement tables 1 and 2

(age, parity [>=2], Black ethnicity, SBP, DBP, triceps skinfold, total sum of skinfold and adiponectin)

	Odds Ratio	Std. Error	z	P>|z|	95% Conf. Interval
Log adiponectin	0.179	0.120	-2.57	0.010	0.048 to 0.666
Age	1.148	0.075	2.11	0.035	1.010 to 1.305
Parity ≥2	3.382	2.597	1.59	0.113	0.751 to 15.236
Black ethnicity	0.795	0.545	-0.33	0.738	0.207 to 3.048
SBP	1.004	0.050	0.08	0.932	0.912 to 1.106
DBP	1.092	0.058	1.66	0.098	0.984 to 1.212
Triceps skinfold	1.072	0.047	1.58	0.115	0.983 to 1.169
Total skinfold	1.005	0.023	0.22	0.823	0.961 to 1.051