The potential role of biomarkers in predicting gestational diabetes

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Abstract

Gestational diabetes (GD) is a frequent complication during pregnancy and is associated with maternal and neonatal complications. It is suggested that a disturbing environment for the foetus, such as impaired glucose metabolism during intrauterine life, may result in enduring epigenetic changes leading to increased disease risk in adult life. Hence, early prediction of GD is vital. Current risk prediction models are based on maternal and clinical parameters, lacking a strong predictive value. Adipokines are mainly produced by adipocytes and suggested to be a link between obesity and its cardiovascular complications. Various adipokines, including adiponectin, leptin and TNFα, have shown to be dysregulated in GD. This review aims to outline biomarkers potentially associated with the pathophysiology of GD and discuss the role of integrating predictive biomarkers in current clinical risk prediction models, in order to enhance the identification of those at risk.

Introduction

Gestational diabetes (GD) is defined as any glucose intolerance with onset or first recognition during pregnancy. GD has a prevalence of 7% worldwide, depending on the population studied and diagnostic criteria used (1). The incidence of GD is increasing in line with the global rise of obesity and type 2 diabetes mellitus (T2DM) (2). GD occurs when β-cells cannot compensate for the increased levels of insulin resistance (3). Insulin resistance and β-cell dysfunction are two known mechanisms; however, the exact cellular mechanisms remain to be elucidated (4). GD is associated with maternal and neonatal short- and long-term complications (5, 6). For the offspring, this includes a predisposition for development of obesity and T2DM (7, 8). Long-term maternal risks include T2DM and cardiovascular disease (9). Currently, the GD diagnosis is made during the late second trimester, possibly exposing the infant to intrauterine metabolic alterations and epigenetic programming for a significant period of time. Reported evidence suggests that metabolic alterations can predispose infants to long-term pathology (10, 11). Detection and management of GD in pregnancy can reduce the frequency of adverse pregnancy outcome (12, 13). Hence, there is need to predict and detect GD earlier in pregnancy in order to limit the exposure to impaired glucose metabolism. Investigating the role of adipokines associated with the pathophysiology of GD has gained interest (14, 15). In recent years, adipokines have been posed as the link between adiposity and adverse complications such as insulin resistance. Identification of early biomarkers in pregnant women, who subsequently develop GD, may result in improved understanding of GD pathogenesis. Combining biomarkers and risk factors into...
a predictive model may add to early prediction of GD, evoke effective prevention strategies and may ultimately reduce complications associated with GD.

The aim of this review is to (1) identify potential predictive biomarkers in GD and (2) discuss the role of incorporating predictive biomarkers into clinical risk prediction models, for the stratification of high-risk patients.

Epigenetic footprint

Metabolic alterations such as impaired glycaemic control during foetal development can lead to functional and structural alterations in the foetus, resulting in a predisposition for developing chronic metabolic diseases later in life. These alterations are also referred to as ‘foetal programming’ and they can cause epigenetic changes (10).

Epigenetic changes ascribe to the change in the biochemical structure of DNA that ultimately alters gene expression. This includes DNA methylation, histone modification and non-coding RNA processes (16). Epigenetic changes have been observed in many disease states and offer biochemical evidence of the detrimental effects of adverse developmental conditions and subsequent disease (10). This relationship has been supported by epidemiologic and animal studies (17, 18, 19, 20). Furthermore, it has been reported that maternal insulin resistance also causes insulin resistance in the foetus, as early as the embryonic stage (21). Multiple studies have linked maternal GD with the development of obesity and T2DM in children (11, 22), who are eight times more likely to develop T2DM than non-GD children (23). Therefore, there is a strong need for early detection of GD. Detection preceding the hyperglycaemia might avoid subsequent harm. Investigating early predictive biomarkers in GD may be a step in this direction.

Obesity, inflammation and GD

More women of childbearing age are entering pregnancy being overweight or obese (24). Obese pregnant women have a three-fold risk for developing GD (25). The global increase in GD is largely attributed to the ongoing obesity pandemic (26). Obesity is characterized by altered production of proinflammatory cytokines by adipocytes causing a state of chronic low-grade inflammation (27). It drives the expression and production of proinflammatory (TNF-alpha and IL-6) and anti-inflammatory cytokines or adipokines (adiponectin, leptin and visfatin) (28). Adipokines have a clear regulatory role in metabolism, including modifying insulin secretion and sensitivity, appetite, energy control and inflammation (29). Clinical and epidemiologic studies have described a sound relationship between obesity, chronic low-grade inflammation and the development of T2DM (30). In normal pregnancy, the immune system is subjected to changes with a delicate balance between production of pro- and anti-inflammatory cytokines. Pregnancies in obese individuals further enhance the proinflammatory profile leading to an imbalance and, therefore, possible complications. It is increasingly being recognized that inflammation is also a feature of GD (31, 32). In GD, a proinflammatory state prevails and the increased production of proinflammatory cytokines debilitates insulin signalling (33). Previously, it has been reported that a downregulation of adiponectin and anti-inflammatory markers such as IL-6 and IL-10 and an enhanced production of proinflammatory cytokines such as IL-6 and TNF-alpha can be observed in GD (33, 34).

Adipokines

Adiponectin

Adiponectin is an adipocyte-derived protein. It contains anti-atherogenic, anti-inflammatory and insulin-sensitizing properties (35). Adiponectin is inversely correlated with obesity, hypertension, serum lipids and coronary artery disease (35, 36). Decreased adiponectin levels have also been associated with an increased risk of T2DM (37, 38). Adiponectin levels are known to decrease progressively during normal pregnancies, probably in response to decreased insulin sensitivity (39). Several studies have also shown reduced adiponectin levels during mid-pregnancy (24–28 weeks) in GD compared with controls (40, 41, 42, 43, 44, 45), relating low levels of adiponectin to the onset of insulin resistance and diminished B-cell function (46). A systematic review and meta-analysis of adiponectin concentrations in 560 GD patients and 781 controls underlined a significantly decreased adiponectin level in GD patients vs controls (45). However, it must be noted that results are in light of a significant heterogeneity among the included studies. In recent years, prospective studies have addressed the role of adiponectin as a possible early predictor of GD. Lower levels of adiponectin in the first trimester of pregnancy are associated with a greater risk for developing GD (47, 48, 49), suggesting that a downregulation of
adiponectin may be a predictor of GD. However, in a systematic review and meta-analysis, adiponectin had a moderate effect for predicting future GD with pooled diagnostic odds ratio (DOR) of 6.4 (95% CI: 4.1, 9.9), a summary sensitivity of 64.7% (95% CI: 51.0%, 76.4%) and a specificity of 77.8% (95% CI: 66.4%, 86.1%) (50). Furthermore, a nested case–control study showed that low pre-pregnancy adiponectin levels are associated with a 5.0-fold increased risk of developing GD (51). This association remained significant after adjusting for known risk factors for GD. This might be relevant for clinical practice as it identifies a group of high-risk women that might otherwise not have been identified. Adiponectin therapy has been tested in animal models of obesity and it has been shown to improve glycemia and reduce hyperinsulinaemia without alterations in body weight (52).

In summary, lower levels of adiponectin are linked to obesity, type 2 diabetes and GD. Adiponectin might play a role in the pathophysiology of GD and can be seen as a promising predictive biomarker for GD. Further research addressing lifestyle interventions or adiponectin intervention therapy is needed to further establish the role of adiponectin in GD.

**Leptin**

Leptin is an adipocyte-derived hormone. It is predominantly produced by adipocytes but is also produced in ovaries and the placenta. It regulates energy balance through hypothalamic pathways (53). Increased leptin concentrations are associated with weight gain, obesity and hyperinsulinaemia (54). Maternal leptin levels are known to increase two- to three-fold in pregnancy, likely due to placental secretion (55). Increased leptin levels have been reported in women with GD (45). Inflammatory markers such as IL-6 and TNF-α probably also play a role in the pathophysiology of GD by promoting chronic low-grade inflammation, while further increasing leptin concentrations (56). A prospective cohort study reported increased concentrations of leptin before 16 weeks of gestation, independent of adiposity, which were associated with an increased risk of GD (57). Another small study showed that leptin was increased in all women during pregnancy, with the highest concentrations in obese GD subjects. Adjusted for fat mass, this correlation disappeared, however (33). Generally speaking, current evidence is limited, in part due to confounding effects of measures of adiposity. Leptin is likely to be involved in the pathophysiology of GD but appears to be a poor predictor of GD.

**Visfatin**

Visfatin is an adipokine and is mostly produced by visceral fat. It has endocrine, paracrine and autocrine actions (58). Increased visfatin levels have been reported in obesity, metabolic syndrome and T2DM (59, 60). In pregnancy, visfatin levels progressively increase up to the second trimester, after which they decrease again with the lowest concentrations observed in the third trimester (61). In GD, reports on visfatin levels have thus far been inconsistent, as both decreased and increased levels have been reported (62, 63, 64). Another study showed that visfatin measured in the first trimester was better in the prediction of GD compared with CRP, IL-6, adiponectin and leptin (65). In a case–control study, visfatin levels measured in the first trimester were increased in the GD group, but when added to other maternal risk factors, the GD detection rate did not improve (66). Results thus far suggest that visfatin is a potential biomarker in GD, but additional prospective studies are definitely needed to further investigate the relationship between visfatin and GD.

**Resistin**

Resistin is an adipocyte-derived hormone expressed by monocytes, macrophages and adipocytes (67). Resistin is positively associated with adiposity. Resistin levels are known to increase during pregnancy, probably due to weight gain (56, 68). A potential link between resistin, adiposity and insulin resistance in pregnancy might exist but to date remains inconclusive due to conflicting reports from case–control studies (69, 70). Nested case–control studies, investigating resistin levels in early pregnancy, found no differences in resistin levels between GD and controls (adjusted for BMI) (34, 49). A prospective study with larger sample size than the previous case–control studies also showed no significant association between resistin and GD (71). Other studies have shown elevated maternal levels of resistin in GD (68, 69, 72). A systematic review showed no significant association between resistin levels and GD pregnancies (73). Significant heterogeneity among studies was a major issue in the analysis. Currently, there is no sound evidence that resistin is involved in the pathophysiology or prediction of GD.
Other inflammatory mediators

TNFα

TNFα is a proinflammatory cytokine and is produced by monocytes and macrophages. It affects insulin sensitivity and secretion through impairing B-cell function and insulin signalling pathways, resulting in insulin resistance and possibly GD (74). Multiple studies have reported increased maternal TNFα levels in subjects with GD, predominantly in late pregnancy (75, 76, 77). A meta-analysis also showed increased TNF-α levels in GD vs controls. Subgroup analysis revealed that this relationship remained significant when compared with BMI-matched controls (45). The increased levels are thought to be due to increased oxidative stress and inflammation associated with impaired glucose metabolism (78). A small nested case–control study with only 14 cases and 14 controls addressing the predictive value of TNFα showed no differences between women with GD and controls (34). In a prospective study in GD and controls, TNFα levels were measured pre-gravid, at 12–14 weeks and 34–36 weeks. TNFα levels were increased at 34–36 weeks of gestation and were inversely correlated with insulin sensitivity (33). Further prospective studies are required to investigate the predictive value of TNFα in GD, adjusting for measures of adiposity.

High-sensitivity C-reactive protein (hsCRP)

hsCRP is an acute-phase protein and is produced in response to tissue injury, inflammation and infection. CRP has been shown to be associated with obesity and diabetes mellitus. In turn, it is well known that obesity is associated with inflammation, which contributes to insulin resistance. Elevated first-trimester CRP levels are associated with GD risk (P for trend=0.007). After adjusting for pre-pregnancy BMI, family history of DM and nulliparity, women with CRP in the highest quartile had a 3.5-fold increased risk of GD compared with those in the lowest quartile (32). Wolf and coworkers also reported that first-trimester CRP levels were significantly increased among women who subsequently developed GD compared with control subjects (3.1 vs 2.1 mg/L, P<0.01) (31). After adjusting for age, race/ethnicity, smoking, parity, blood pressure and gestational age at CRP sampling, the increased risk of developing GD among women in the highest tertile compared with the lowest tertile was 3.6 times higher (95% CI: 1.2–11.4). When adjusted for BMI, this association was not found anymore, however (79).

Berggren and coworkers evaluated whether first-trimester hsCRP was predictive for third-trimester impaired glucose tolerance (IGT). hsCRP was positively associated with IGT, but, again, the association disappeared when adjusted for BMI (80). Thus far, the positive association of (hs)CRP and GD seems to be in part mediated by BMI.

Sex hormone-binding globulin (SHBG)

SHBG is a glycoprotein and plays a role in the regulation and transport of sex hormones. In vitro, SHBG has been proposed as a marker in insulin resistance as it has shown that insulin and insulin-like growth factor cause inhibition of SHBG secretion (81). Indeed, a relationship between low levels of SHBG and T2DM has been reported (82). A prospective cross-sectional study evaluating the serum SHBG levels reported that SHBG concentrations were significantly lower in GD subjects than in normal pregnancies (83). Furthermore, in women who were treated with insulin, SHBG levels were reported to be even lower (84). This might suggest that SHBG could help to differentiate or predict the women who will require insulin therapy. The overall additional clinical and predictive value of these results is limited as testing on GD is already routinely performed at this stage of pregnancy. A prospective observational study (n=269) evaluating several biomarkers earlier than 15 weeks of gestation showed that low levels of SHBG were associated with an increased risk of GD. This association was independent of other risk factors (BMI, smoking and blood pressure). Using the cut-off value of 211.5 mmol/L, SHBG showed an acceptable sensitivity of 85% but a low specificity of 37%. Adding hs-CRP increases the specificity to 75.46%, however (85). Another prospective cross-sectional study, addressing the predictive value of SHBG for the diagnosis of GD, reported that low levels of SHBG assessed between 13 and 16 weeks of gestation were positively associated with the development of GD (n=30) (P<0.01) (86). A limitation in this study, however, was that they could not establish an SHBG cut-off value for a constant term of pregnancy. A nested case–control study showed that non-fasting SHBG in the first trimester was consistently associated with an increased risk for GD (15).

Other potential biomarkers

Adipocyte fatty acid-binding protein (AFABP) is an independent risk predictor for metabolic syndrome, T2DM and cardiovascular disease (87). Two studies...
have reported increased concentrations in GD (88, 89). Studies investigating the predictive value of AFAP in GD have not been performed to date, however. IL-6 is a proinflammatory cytokine and is increased in obesity and associated with indices of adiposity and insulin resistance, such as body mass index (BMI) (90, 91). Controversy exists regarding the changes in circulating levels of IL-6 in obesity. The relationship between IL-6 and insulin action appears to be regulated via adiposity (92). However, in a case–control study, plasma IL-6 levels have shown to be elevated when adjusted for BMI in women with GD (93). Low levels of vitamin D have been associated in obesity and type 2 diabetes. In pregnancy, low levels are also often observed (94). Low vitamin D levels in the first trimester were also associated with a higher risk for GD (adjusted for confounders and risk factors) (94). Recent meta-analyses have supported this finding, but the included studies were not all randomized controlled (95). Future RCTs are needed to further clarify the predictive role of vitamin D.

Clinical prediction models incorporating biomarkers

Current screening methods only identify women who already have impaired glucose metabolism. Ideally, subjects with high risk of GD should be identified before they exceed the oral glucose tolerance test (OGTT) threshold values. Early prediction would allow for timely intervention that could limit gestational weight gain and obesity and possibly the onset of GD. Current screening methods have moderate detection rates (96, 97). Clinical risk prediction models have been investigated in GD. For example, the development of GD can be predicted from the ethnicity, family history, history of GD and body mass index. The model showed an area under the receiver operating characteristic curve of 0.77 (95% CI: 0.69–0.85) (98). If an OGTT was performed in all women with a predicted probability of 2% or more, 43% of all women would be tested and 75% of the women with GD would be identified (98). Furthermore, in a large prospective cohort (n=7929), the best performing model, based on ethnicity, BMI, family history of diabetes and history of GD, showed a sensitivity, specificity and AUC of 73% (66–79), 81% (80–82) and 0.824 (0.793–0.855), respectively, for the identification of GD cases requiring insulin therapy (99). Introducing biomarkers to a set of clinical risk factors may enhance predication rates. For example, tissue plasminogen activator (t-PA) and low HDL cholesterol were independent significant predictors of GD. The addition of these biomarkers to a set of demographic and clinical risk factors increased the area under the curve (ROC) from 0.824 to 0.861 (100). t-PA in the prediction of GD is a novel finding, but previous work has shown that t-PA is associated with an increased risk of T2DM (101). Another study demonstrated that elevated plasma insulin and reduced adiponectin levels in the first trimester improved GD identification rates compared with clinical factors alone (34). Maternal risk factors alone showed a prediction rate of 61% for GD, adding adiponectin and SHBG increased detection rates to 74% (14). Investigators in another study showed that adding adiponectin to a set of clinical risk factors increased the area under the receiver operating curve increased significantly (102). Adding maternal visfatin and adiponectin to a set of maternal risk factors showed a detection rate of 68% (95% CI: 58.3–76.3%) (66). The clinical implementation of such multi-parametric prediction models depends on significant reduction in adverse pregnancy outcomes, practical acceptability and cost-effectiveness. Ultimately, these models require prospective validation studies and further identification of predictive threshold values for these biomarkers.

Conclusion

Gestational diabetes is currently detected in late pregnancy, unnecessarily exposing the infant to harmful intrauterine conditions. There is a definite clinical need to better predict and detect GD early in pregnancy in order to prevent further harm to mother and child. Adiponectin is probably one of the most promising candidate in the prediction of GD. The clinical value of implementing a combined clinical model is questionable as the current level of evidence is weak due to study design, differences in diagnostic criteria and assay methods used. Well-designed prospective studies addressing current limitations are needed to identify reliable predictive biomarkers in GD and their additional value to current clinical prediction tools.

Declaration of interest

Huguette S Brink, Aart Jan van der Lely and Joke van der Linden have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.
Stressful life events during pregnancy, such as severe maternal diabetes, may interfere with the normal development of the offspring's placenta. This can affect fetal programming, where the developing fetus is exposed to the maternal environment and experiences the impact of such events. Several studies have shown that gestational diabetes mellitus (GDM) is associated with an increased risk of type 2 diabetes and metabolic syndrome in the offspring. A review by Horvath et al. suggests that maternal diabetes and perinatal programming can lead to a reduced metabolic reserve in the offspring, which may influence the risk of developing metabolic disorders.

In a study conducted by Clauws et al., it was found that maternal diabetes during pregnancy is associated with an increased risk of metabolic disorder in the offspring. This risk appears to be more pronounced in women who have a family history of diabetes. The review by Chiesi et al. highlights the role of early life programming in the development of metabolic disorders and the importance of understanding the mechanisms underlying the increased risk of diabetes in the offspring of diabetic mothers.

The effects of maternal diabetes on the offspring's development are complex and multifactorial. Further research is needed to understand the underlying mechanisms and to develop strategies for preventing the deleterious effects of maternal diabetes on the offspring's health.
Biomarkers in the prediction of gestational diabetes mellitus

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Adipose tissue as an endocrine organ. Molecular and Cellular Endocrinology 2010 316 129–139. (doi:10.1016/j.mce.2009.08.018)

Spranger J, Kroke A, Mohlig M, Bergmann MM, Ristow M, Boeing H & Pfeiffer AF. Adiponectin and protection against type 2 diabetes mellitus. Lancet 2003 361 226–228. (doi:10.1016/S0140-6736(03)12255-6)

Nakashima R, Kamei N, Yamane K, Nakanishi S, Nakashima A & Kohno N. Decreased total and high molecular weight adiponectin are independent risk factors for the development of type 2 diabetes in Japanese-Americans. Journal of Clinical Endocrinology and Metabolism 2006 91 3873–3877. (doi:10.1207/s15327965jecm9105_1)

Galic S, Oakhill JS & Steinberg GR. Adipose tissue as an endocrine organ. Molecular and Cellular Endocrinology 2010 316 129–139. (doi:10.1016/j.mce.2009.08.018)

Doruk M, Ugar M, Oruc AS, Demirel N & Yildiz Y. Serum adiponectin in gestational diabetes and its relation to pregnancy outcome. Journal of Obstetrics and Gynecology 2014 34 471–475. (doi:10.3109/01446351.2014.902430)

Pala HG, Ozalp Y, Yener AS, Gercelkligil G, Uysal S & Onural A. Adiponectin levels in gestational diabetes mellitus and in pregnant women without glucose intolerance. Advances in Clinical and Experimental Medicine 2015 24 85–92. (doi:10.17210/ajcem/2014(08)141)

Tsai PJ, Yu CH, Hsu SP, Lee YH, Huang IT, Ho SC & Chu CH. Serum adiponectin concentration in normal pregnancy. Nutrition 2005 21 1095–1099. (doi:10.1016/j.nut.2005.03.008)

Soheilykhah S, Mohammad M, Mojibian M, Rahimi-Saghari S, Rashidi M, Hadimoueshani H & Afkhami-Ardekan M. Maternal serum adiponectin concentration in gestational diabetes. Gynecological Endocrinology 2009 25 593–596. (doi:10.1080/09513590902972109)

Ramirez VI, Miller E, Meireles CL, Gelfond J, Krummel DA & Powell TL. Adiponectin and IGF-1 in the development of gestational diabetes in obese women. BMJ Open Diabetes Research & Care 2014 2 e000110. (doi:10.1136/bmjdrc-2013-000110)

Xu J, Zhao YH, Chen VP, Yuan XL, Wang J, Zhu H & Lu CM. Maternal circulating concentrations of tumor necrosis factor-alpha, leptin, and adiponectin in gestational diabetes mellitus: a systematic review and meta-analysis. Scientific World Journal 2014 2014 926932. (doi:10.1155/2014/926932)

Wojcik M, Chmielewska-Kassiarz M, Gryzwniczok K, Wozniak L & Cypryk K. The relationship between adipose tissue-derived hormones and gestational diabetes mellitus (GDM). Endokrynologia Polska 2014 65 134–142. (doi:10.5603/EP.2014.0019)

Lacroix M, Battista MC, Doyon M, Menard J, Ardidoule JZ, Perron P & Hivert MF. 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 1577–1583. (doi:10.2337/dc12-1731)

Williams MA, Qiu C, Muy-Rivera M, Vadack稽skaia S, Song T & Luthy DA. Plasma adiponectin concentrations in early pregnancy and subsequent risk of gestational diabetes mellitus. Journal of Clinical Endocrinology and Metabolism 2004 89 2306–2311. (doi:10.1210/jc.2003-031201)

Lain KY, Daftary AR, Ness RB & Roberts JM. First trimester adipocytokine concentrations and risk of developing gestational diabetes later in pregnancy. Clinical Endocrinology 2008 69 407–411. (doi:10.1111/j.1365-2265.2008.03198.x)

Ilidromiti S, Sassarini J, Kelsey TW, Lindsay RS, Sattar N & Nelson SM. Accuracy of circulating adiponectin for predicting gestational diabetes: a systematic review and meta-analysis. Diabetologia 2016 59 692–699. (doi:10.1007/s00125-015-3855-6)

Heddderson MM, Darbinian J, Havel PJ, Quesenberry CP, Sridhar S, Ehrlich S & Ferrara A. Low pre-pregnancy adiponectin concentrations are associated with a marked increase in risk for development of gestational diabetes mellitus. Diabetes Care 2013 36 3930–3937. (doi:10.2337/dc13-089)

Ukkola O & Santaniemi M. Adiponectin: a link between excess adiposity and associated comorbidities? Journal of Molecular Medicine 2002 80 696–702. (doi:10.1007/s00109-002-0378-7)

Wauters M, Considine RV & Van Gaal LF. Human leptin: from an adipocyte hormone to an endocrine mediator. European Journal of Endocrinology 2000 143 293–311. (doi:10.1530/eje.0.1430293)

Fasshauer M, Bluher M & Stumvoll M. Adipokines in gestational diabetes. Lancet Diabetes & Endocrinology 2014 2 488–499. (doi:10.1016/s2213-8587(13)07176-1)

Briana DD & Malamitsi-Puchner A. Reviews: adipocytokines in normal and complicated pregnancies. Reproductive Sciences 2009 16 921–937. (doi:10.1177/193259030936614)

Miehle K, Stepan H & Fasshauer M. Leptin, adiponectin and other adipokines in gestational diabetes mellitus and pre-eclampsia. Clinical Endocrinology 2012 76 2–11. (doi:10.1111/j.1365-2265.2011.04234.x)

Qiu C, Williams MA, Vadack稽skaia S, Frederick IO & Luthy DA. Increased maternal plasma leptin in early pregnancy and risk of gestational diabetes mellitus. Oestrogens & Gynecology 2004 103 519–525. (doi:10.1016/j.aog.2000.11.0362.53602.7a)

Adeghate E. Visfatin: structure, function and relation to diabetes mellitus and other dysfunctions. Current Medicinal Chemistry 2008 15 1851–1862. (doi:10.2174/092986708785133004)

Filippatos TD, Derdemizis CS, Gazi IE, Lagos K, Kiortsis DN, Tselipis AD & Eliaf MS. Increased plasma visfatin levels in subjects with the metabolic syndrome. European Journal of Clinical Investigation 2008 38 71–72. (doi:10.1111/j.1365-2362.2007.01904.x)

Chen MP, Chung FM, Chang DM, Tsai JC, Huang HF, Shin SJ & Lee YJ. Elevated plasma level of visfatin/pre-B cell colony-enhancing factor in patients with type 2 diabetes mellitus. Journal of Clinical Endocrinology and Metabolism 2006 91 295–299. (doi:10.1210/jc.2005-1475)

Mazaki-Tovi S, Romero R, Kusavinovic JP, Vaisbuch E, Erez O, Than NG, Chaiworapongsa T, Nhan-Chang CL, Facora P, Gotsch F, et al. Maternal visfatin concentration in normal pregnancy. Journal of Reproductive Medicine 2009 54 206–217. (doi:10.1515/jpm.2009.054)

Lewandowski CK, Stojanovic N, Press M, Tuck SM, Szosland K, Bienkiewicz M, Vatish M, Lewinski A, Prelevic GM & Randeva HS. Elevated serum levels of visfatin in gestational diabetes: a comparative study across various degrees of glucose tolerance. Diabetologia 2007 50 1033–1037. (doi:10.1007/s00125-007-0610-7)

Krzyzanowska K, Krugluger W, Mittermayer F, Baumann R, Haider D, Shnawa N & Schernthaner G. Increased visfatin concentrations in
women with gestational diabetes mellitus. Clinical Science 2006 110 605–609. (doi:10.1042/CS20060363)

64 Akturk M, Altinova AE, Mert I, Buyukkagaci U, Sargin A, Arslan M & Danisman N. Visfatin concentration is decreased in women with gestational diabetes mellitus in the third trimester. Journal of Endocrinological Investigation 2008 31 610–613. (doi:10.1007/ BF03345611)

65 Mastorakos G, Valsamakis G, Papatheodorou DC, Barlas I, Margeli A, Boutsisadis A, Kouskouvi E, Vitoratos N, Papadimitriou A, Papasotiriou I, et al. The role of adipokynes in insulin resistance in normal pregnancy: visfatin concentrations in early pregnancy predict insulin sensitivity. Clinical Chemistry 2007 53 1477–1483. (doi:10.1373/clinchem.2006.084731)

66 Ferreira AF, Rezende JC, Vaikousi E, Akolekar R & Nicolaides KH. Maternal serum visfatin at 11–13 weeks of gestation in gestational diabetes mellitus. Clinical Chemistry 2011 57 609–613. (doi:10.1373/clinchem.2010.159806)

67 Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS & Lazar MA. The hormone resistin links obesity to diabetes. Nature 2001 409 307–312. (doi:10.1038/35053000)

68 Palik E, Baranyi G, Melczer Z, Audikovszky M, Szocs A, Winkler G & Cseh K. Elevated serum acylated (biologically active) ghrelin and resistin levels are associated with pregnancy-induced weight gain and insulin resistance. Diabetes Research and Clinical Practice 2007 76 351–357. (doi:10.1016/j.diabres.2006.09.005)

69 Cortelazzi D, Corbetta S, Ronzoni S, Pelle E, Marconi A, Cozzi V, Cetin I, Cortelazzi R, Beck-Peccoz P & Spada A. Maternal and foetal resistin and adiponectin concentrations in normal and complicated pregnancies. Clinical Endocrinology 2007 66 447–453. (doi:10.1111/j.1365-2265.2007.03276.x)

70 Kuzmicki M, Telejko B, Szamatowicz J, Zonenberg A, Nikolajuk Kuzmicki M, Telejko B, Szamatowicz J, Zonenberg A, Nikolajuk C, Kralisch S, Stepan H, Kratzsch J, Verlohren M, Verlohren HJ, Drynda BF03345611)

71 Lowe LP, Metzger BE, Lowe WL Jr, Dyer AR, McDade TW, McIntyre HD & HAPPO Study Cooperative Research Group. Inflammatory mediators and glucose in pregnancy: results from a subset of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. Journal of Clinical Endocrinology and Metabolism 2010 95 5427–5434. (doi:10.1210/jc.2010-1662)

72 Megia A, Vendrell J, Gutierrez C, Sabate M, Broch M, Fernandez-Real JM & Simon I. Insulin sensitivity and resistin levels in gestational diabetes mellitus and after parturrition. European Journal of Endocrinology 2008 158 173–178. (doi:10.1530/EJEndo-07-0671)

73 Lobo TF, Torloni MR, Gueuvoghlanian-Silva BY, Mattar R & Daher V. Elevated levels of interleukin-6 are reduced in serum of patients with gestational diabetes mellitus. Experimental and Clinical Endocrinology & Diabetes 2007 115 365–369. (doi:10.1055/s-2007-993073)

74 Taglianti S, Fasshauer M. Adipocyte fatty acid binding protein: a novel adipokine involved in the pathogenesis of metabolic and cardiovascular disease? Diabetesologia 2013 56 10–21. (doi:10.1007/51252-012-2737-4)

75 Ortega-Senovilla H, Schaefer-Gruf U, Meitzner K, Abou-Dakn M, Graf K, Kuntscher U & Herrera J. Gestational diabetes causes changes in the concentrations of adipocyte fatty acid-binding protein and other adipokynes in cord blood. Diabetes Care 2011 34 1365–1366. (doi:10.2337/dc10-2175)

76 Kralisch S, Stepan H, Kratzsch J, Verlohren M, Verlohren HJ, Drynda BF03345611)

77 Vgontzas AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K & Chrousos GP. Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. Journal of Clinical Endocrinology and Metabolism 1997 82 1313–1316. (doi:10.1210/jcem.82.5.3950)

78 Bastard JP, Jardel C, Bruckert E, Blondy P, Capeau J, Laville M, Vidal H & Hainque B. Elevated levels of interleukin-6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. Journal of Clinical Endocrinology and Metabolism 2000 85 3338–3342. (doi:10.1210/jcem.85.9.3338)

79 Vogtanz AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K & Chrousos GP. Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. Obesity Research 2001 9 414–417. (doi:10.1038/oby.2001.54)

80 Merisotis AS, Duhe MC, Cote JA, Robitaille J, Weissagel SJ & Thenerof A. Circulating interleukin-6 concentrations during and after gestational diabetes mellitus. Acta Obsetetrica et Gynecologica Scandinavica 2000 79 839–845. (doi:10.1034/j.1600-124X.2000.79020839.x)

81 Hu J, Zhang A, Yang S, Wang Y, Goswami R, Zhou H, Wang Z, Li R, Cheng Q, Zhen Q, et al. Combined effects of sex hormone-binding globulin and sex hormones on risk of incident type 2 diabetes. Journal of Diabetes 2015 5 508–515. (doi:10.1111/1753-0407.12322)

82 Bartha JL, Camino-Delgado R, Romero-Carmona R & Gomez-Jaen MC. Sex hormone-binding globulin in gestational diabetes. Acta Obsetretica et Gynecologia Scandinavica 2000 79 839–845. (doi:10.1034/j.1600-124X.2000.79020839.x)

83 Kralisch S & Fasshauer M. Adipocyte fatty acid binding protein: a novel adipokine involved in the pathogenesis of metabolic and cardiovascular disease? Diabetesologia 2013 56 10–21. (doi:10.1007/51252-012-2737-4)
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94 Lacroix M, Battista MC, Doyon M, Houde G, Menard J, Ardilouze JL, Hivert M-F, Perron P, Hivert M-F, Perron P, et al. Lower vitamin D levels at first trimester are associated with higher risk of developing gestational diabetes mellitus. Acta Diabetologica 2014 51 609–616. (doi:10.1007/s00592-014-0564-4)

95 Zhang MX, Pan GT, Guo JF, Li BY, Qin LQ & Zhang ZL. Vitamin D deficiency increases the risk of gestational diabetes mellitus: a meta-analysis of observational studies. Nutrients 2015 7 8366–8375. (doi:10.3390/nu7105398)

96 Scott DA, Loveman E, McIntyre L & Waugh N. Screening for gestational diabetes: a systematic review and economic evaluation. Health Technology Assessment 2002 6 1–161. (doi:10.3310/hta6110)

97 Waugh N, Royle P, Clar C, Henderson R, Cummins E, Hadden D, Lindsay R & Pearson D. Screening for hyperglycaemia in pregnancy: a rapid update for the National Screening Committee. Health Technology Assessment 2010 14 1–183. (doi:10.3310/hta14450)

98 van Leeuwen M, Opmeer BC, Zweers EJ, van Ballegooie E, ter Brugge HG, de Valk HW, Visser GHA & Mol BWJ. Estimating the risk of gestational diabetes mellitus: a clinical prediction model based on patient characteristics and medical history. BJOG 2010 117 69–75. (doi:10.1111/j.1471-0528.2009.02425.x)

99 Theriault S, Forest JC, Masse J & Giguet Y. Validation of early risk-prediction models for gestational diabetes based on clinical characteristics. Diabetes Research and Clinical Practice 2014 103 419–425. (doi:10.1016/j.diabres.2013.12.009)

100 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 3017–3022. (doi:10.2337/db10-0688)

101 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 31 995–1000. (doi:10.2337/dc07-1549)

102 Maitland RA, Seed PT, Briley AL, Homsy M, Thomas S, Pasapathy D, Robson SC, Nelson SM, Sattar N, Poston L, et al. Prediction of gestational diabetes in obese pregnant women from the UK Pregnancies Better Eating and Activity (UPBEAT) pilot trial. Diabetic Medicine 2014 31 963–970. (doi:10.1111/dme.12482)

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