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.

Key Words
- adipokines
- biomarkers
- gestational diabetes
- prediction

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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

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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-4 and IL-10 and an enhanced production of proinflammatory cytokines such as IL-6 and TNF-α 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

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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 glycaemia 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 adipose-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.

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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

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have reported increased concentrations in GD (88, 89). Studies investigating the predictive value of AFABP 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.

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