Chapter

Biomarkers in GDM, Role in Early Detection and Prevention

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Abstract

Gestational Diabetes Mellitus (GDM) happens to be a very frequent and major complication of pregnancy because of higher morbidity and mortality, both for the mother and the baby. After delivery, GDM carries the risk of higher maternal morbidity due to post pregnancy obesity, development of diabetes mellitus, obesity and also cardiovascular diseases in significant number in both the mother and child for future. As per current guidelines, GDM is diagnosed at the end of the second trimester by elevated blood glucose values when, foetal damages by metabolic and epigenetic changes had already started. As a result, treatments cannot be started before the late second or third trimester, when the process of high risk of foetal morbidity and mortality has been set in. If by any method we can predict development of GDM at earliest part of first trimester or even more overjealously, we can predict, before pregnancy, then and then only we can avoid many disasters induced by GDM. With this idea many biomarkers, both clinical and laboratory based like clinical, metabolic, inflammatory and genetic markers etc., related with early pregnancy metabolic alterations have been studied for their potential to help in the prediction of later pregnancy glucose intolerance. Though promises are seen with some biomarker-enhanced risk prediction models for GDM, but lack of external validation and translation into day-to-day clinical applications, cost effectiveness, with which they may be utilized in routine prenatal care has limited their clinical use. But future is very promising and incorporating the biomarkers which precede the onset of hyperglycaemia into a risk prediction model for GDM and may help us for earlier risk assessment, screening, and diagnosis of GDM and also prevention of its both the immediate and remote complications. This review highlights the current knowledge of the understanding of the candidacy and practical utility of these biomarkers for GDM with recommendations for further research.

Keywords: Biomarkers, gestational diabetes mellitus (GDM), macrosomia, foetal abnormalities

1. Introduction

Norman Freinkel once told that "No single period in human development, provides a greater potential (than pregnancy) for long – range 'pay – off' via a relatively short – range period of enlightened metabolic manipulation".

During pregnancy, the body systems of the woman, must support nutrient and oxygen supply for the proper growth and development of the foetus and subsequently during lactation. Inability to adopt the changes in maternal physiology may lead to complications, such as gestational diabetes mellitus (GDM). The

International Association of Diabetes and Pregnancy Study Groups (IADPSG) shows that, GDM may complicate 15–20% pregnancies, and has increased in the last 20 years in all ethnic groups as much as 27% [1].

GDM originates from interplay of factors like specific gene mutations, dysregulation of placental hormones and β-cell injury, favored by advanced age, gynecological alterations and diabetogenic factors. GDM mostly develop after the 2nd trimester of pregnancy, between the 24th and the 28th week of gestation. GDM may precipitate serious and long-term complications for foetal and maternal health, in particular, metabolism and cardiovascular in nature [2].

Currently, in most cases, the diagnosis of Gestational Diabetes Mellitus (GDM) is done around the late phase of second trimester, which may expose the foetus to the hazards of intrauterine metabolic alterations and also epigenetic changes for the period of exposure. Many documented evidences indicate that the metabolic alterations may subject the new born vulnerable to many long-term pathologies. Detection and management of GDM in pregnancy, can reduce the frequency of adverse pregnancy outcome. Hence, we need to predict and identify GDM earlier in pregnancy even if possible before the pregnancy, in order to limit the exposure to impaired glucose metabolism.

American Diabetes Association (ADA) recommends initial screening for GDM at 24–28 weeks [3]. But Seshiah V et al. from India has detected 62.1% cases of GDM before 24 weeks. Moreover, if we do not test before 24 weeks, we will miss earliest intervention for all the cases of undetected diabetes existing before pregnancy [4].

The aim of this review was to find out the useful and possible markers or guides to detect GDM early in pregnancy before rise of blood sugar and if possible, even before pregnancy to avoid all complication for mother and child arising from effects of GDM on gestation.

1.1 Search strategy and selection criteria

References for this review were identified by searching PubMed, Embase for articles in English with no language restrictions for articles published mainly from 2000 to 2021. The search terms used were GDM biomarkers, GDM pathogenesis, GDM prevention and epigenetics of GDM. The final reference list was prepared based on this search, supplemented with references from the authors' own dataset.

2. Biomarkers

GDM develops when beta cell dysfunction coexists, and is complicated by further abnormalities in adipokine and cytokine profiles, increased free fatty acids (FFA), triglycerides (TG), low vitamin D and endothelial dysfunction. The identification of early biomarkers in pregnancy, who may develop GDM, may lead to an improved understanding of pathogenesis of GDM. Combination of biomarkers and different risk factors into a predictive model, may help in early prediction of GDM. This may also find out effective prevention strategies and finally can limit different complications related with GDM. The first-trimester biochemical predictors of GDM are shown in **Table 1**.

3. Epigenetic footprint

Metabolic alterations like impaired glucose control during the phase of foetal development, may result in functional and structural alterations in the developing foetus, and may result in a predispose to the development of chronic metabolic

- Glycemic markers
  - Fasting glucose
  - Post-load glucose
  - Hemoglobin A1C
  - Serum Insulin
  - Tests of insulin sensitivity (HOMA, QUICKI)
- Lipid profile, with higher concentrations of total cholesterol and triglycerides
- Insulin resistance markers
  - Fasting insulin
  - Sex hormone-binding globulin
- Inflammatory markers
  - C-reactive protein
  - Tumor necrosis factor-alpha
  - IL-6
  - TNF-alfa
  - hsCRP
- Genetic markers rs7957197 (HNF1A), rs10814916 (GLIS3), rs3802177 etc.
- Urine biomarkers: l-tryptophan, l-urobilinogen, ceramide (d18:0/23:0), 21-deoxycortisol, cucurbitacin-C, aspartame etc.
- Adipocyte-derived markers
  - Leptin
  - Adiponectin
  - Resistin
  - Visfatin
  - Omentin-1
  - Ghrelin
- Placenta-derived markers
  - Follistatin-like 3
  - Placental growth factor
  - Placental exosomes
  - afamin,
  - fetuin-A,
  - fibroblast growth factors-21/23,
  - ficolin-3 and follistatin,
  - specific micro- RNAs
- Others
  - Vitamin D
  - Glycosylated fibronectin
  - Soluble(pro)renin receptor
  - Alanine aminotransferase
  - Ferritin
  - Glucagon
  - PAI-1
  - Adipocyte fatty acid-binding protein
  - SNPs,
  - DNA methylation,

Table 1.
Showing the first-trimester biochemical predictors of GDM.

diseases in future life. These alterations are actually the 'foetal programming' and may trigger epigenetic changes [5]. The epigenetic changes are considered as different changes in the biochemical structure of DNA, which alters the gene expression in pregnancy as shown in **Table 2**.

Maternal insulin resistance can also cause insulin resistance in the foetus [6]. Multiple studies have correlated maternal GDM, with the development of obesity and T2DM in children who are eight times more prone to develop T2DM than non-GDM children [7, 8]. This raises the strong need for early detection of GDM preceding the hyperglycaemia which might avoid subsequent harm.

- DNA methylation,
- Histone modification
- Non-coding RNA processes.

Table 2.
Showing the epigenetic changes in pregnancy.

4. Obesity, inflammation and GDM

Now a days, more and more women are becoming pregnant, being either overweight or obese. The obese women show a three-fold risk for developing GDM. The global increase in GDM at present time is largely due to the on-going pandemic of obesity. Obesity is related to an altered production of proinflammatory cytokines from the adipocytes, which may lead to a state of chronic low-grade inflammation. It acts upon the expression and production of different proinflammatory cytokines e.g., TNF-alpha and IL-6 and also many anti-inflammatory cytokines. This also produces adipokines e.g., adiponectin, visfatin and leptin etc. Adipokines can modify insulin secretion & sensitivity, appetite, energy control and inflammation. Sound relationship is evident between obesity, chronic low-grade inflammation and development of T2DM. The normal pregnancy shows a balance between the productions of pro-inflammatory and anti-inflammatory cytokines.

Pregnancies in obese women, further may aggravate the proinflammatory markers and may lead to an imbalance and possible complications. It is now accepted that inflammation is also an associated feature of GDM [9]. During GDM, the increased production of proinflammatory cytokines disturbs the insulin signaling [10]. A down regulation 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 are usually observed in GDM [11].

5. Adipocyte-derived markers

5.1 Adipokines or Adiponectin's

Adiponectin is actually an adipocyte protein and consists of anti-atherogenic, anti-inflammatory and also insulin-sensitizing effects [12]. Adiponectin is inversely correlated with the clinical conditions like hypertension, dyslipidaemia, obesity and also coronary artery disease. Diminished level of adiponectin are usually seen with an increased risk of T2DM [13]. During the normal pregnancies, adiponectin decrease progressively also, probably from a decrease in insulin sensitivity [14]. Many studies have indicated that reduced adiponectin levels during 24–28 weeks in GDM compared to non GDM women, probably corelate low levels of adiponectin with onset of insulin resistance and diminished beta cell function [15, 16]. In one study, adiponectin concentrations in 560 GDM patients and 781 controls revealed a significantly decreased adiponectin level in GDM patients vs. controls [17].

Adiponectin, an adipokine having anti-inflammatory, anti-atherosclerotic and insulin-sensitizing proprieties in another study, was constantly lower along the 1st–3rd trimester of GDM gestations [18]. Hypoadiponectinemia increases the risk of developing GDM by 4.6 times [19], and is inversely correlated with the insulin resistance, BMI and leptin [20]. The ratio of plasma adiponectin and leptin (< 0.33) is also considered as predictor of GDM as early as the period of 6th to 14th week of pregnancy [21]. But probably the assessment of the high molecular weight oligomeric-adiponectin may give better results [22].

Recent prospective studies have addressed the role of adiponectin as a possible early predictor of GDM. Lower levels of adiponectin in the first trimester of pregnancy are associated with a greater risk for developing GDM. This suggests that a down regulation of adiponectin may be a predictor of GDM [23]. In a systematic review and meta-analysis, adiponectin had a moderate effect for predicting future GDM [24]. Again, a case–control study found revealed that low adiponectin levels in pre-pregnancy period is associated with an increased risk of 5.0-fold for developing GDM [25].

This association was significant even when adjustment of known risk factors for GDM was done. This is important as it can identify a group of high-risk women, who might be not detected by conventional tests. Therapy with adiponectin in animal models of obesity improves glycaemia and also can reduce hyperinsulinaemia without any changes in body weight [26].

To summarize, a lower level of adiponectin is seen with type 2 diabetes, obesity and GDM. Adiponectin may influence the pathophysiology of GDM and also be a promising predictive biomarker for identifying GDM. Subsequent research for lifestyle interventions or adiponectin therapy should be done to finalize the role of adiponectin and diagnostic ability in cases of GDM particularly during the first trimester of GDM. Serum adiponectin in GDM, when is below <8.9 μg/ml shows an odds ratio of 3.3.

5.2 1,5 Alfa anhydroglucitrol, SHBG

Mean value of 1,5 Alfa anhydroglucitrol level is significantly lower in those destined to develop GDM. In the first trimester, higher SHBG levels are indicating the risk of GDM but this was no longer statistically significant when BMI, ethnicity and family history were considered. A measurement of CRP in the first trimester is not a useful marker of GDM [27].

5.3 Leptin

Leptin is an adipocyte-derived hormone, mostly produced by adipocytes but is also produced in ovaries and the placenta. It regulates energy balance through hypothalamic pathways. Increased leptin is associated with weight gain, obesity and hyperinsulinaemia.

Leptin is a proinflammatory adipokine and participate in immune responses. It also affects glucose metabolism by antagonistic action on appetite and insulin action. In addition, it can stimulate oxidative stress, atherogenesis and arterial stiffness [28]. Leptin levels is detected to be significantly higher in the 2nd half of pregnancy in both normal and overweight women with later diagnosis of GDM [29]. Menon M et al. did a prospective observational study with three study groups, with two-time points-first and second trimester to detect gestational diabetes mellitus as follows: [30]

- Normal glucose tolerance (NGT)
- Gestational diabetes mellitus 1 (GDM1), OGCT done at 1st trimester patients diagnosed as GDM in 1st trimester
- Gestational diabetes mellitus 2 (GDM2), Repeat OGCT done at 2nd trimester patients diagnosed as GDM in 2nd trimester.

They found that found that out of the adipokines, leptin was found to be elevated in GDM2 compared to GDM1 and NGT group with a p value (0.11), adiponectin was reduced only in GDM1 group with p value (0.33), TNFα is almost the same in all the 3 study groups but IL-6 is elevated in first and second trimester GDM group.

Maternal leptin levels increase 2 to 3 times in pregnancy, as a placental secretion. Increased levels of leptin have been seen in GDM.

Inflammatory markers like IL-6 and TNF-α also are involved in the pathophysiology of GDM by promoting both the chronic low-grade inflammation and also leptin concentrations. A prospective study detected elevated values of leptin before

16 weeks of conception, regardless of presence of adiposity and this was accompanied by an increased risk of GDM [31]. In another study leptin was increased in all pregnant women, but with highest concentrations in obese GDM patients [32]. But due to confounding effects of the measures of adiposity, current evidence is limited. Leptin is probably involved in the pathophysiology of GDM but is a poor predictor of GDM.

5.4 Visfatin

Visfatin an adipokine mostly secreted from visceral fat. It possesses both endocrine, paracrine and autocrine effects. Increased level of visfatin is noted in obesity, metabolic syndrome and T2DM. During pregnancy, visfatin levels increase up to the 2nd trimester, then they decrease and persist in lowest concentrations in the third trimester. During GDM, studies on visfatin levels are is inconsistent, as both decreased and increased levels have been reported [33].

In addition to its insulin-like properties to bind to the insulin receptor-1 and promotion of hypoglycaemic effects, visfatin can activate NFκB signaling and chemotaxis and lead to the development of insulin resistance. In fact, visfatin was found increased at the late 1st trimester [34], but differentially expressed at the 3rd trimester of GDM [35].

One study observed, visfatin was better in the prediction of GDM in the first trimester than CRP, IL-6, adiponectin and leptin [36]. One case–control study found that, visfatin in the 1st trimester was higher in GDM, but when it was added to the other maternal risk factors, the GDM detection rate had no improvement [37]. At present, findings indicate that visfatin is a potential biomarker for GDM, but we need further prospective studies to further asses the relationship between visfatin and GDM.

5.5 Resistin

Resistin represents an adipose-derived hormone and is expressed from monocytes, macrophages and adipocytes. It is corelated with high LDL-c and pro-inflammatory molecules and is also positively associated with adiposity. It increases during pregnancy, probably from weight gain. A potential link might exist between resistin, adiposity and insulin resistance during pregnancy, but till now, remains inconclusive as because of conflicting reports from case–control studies [38]. Resistin, is found to be reduced or unchanged during GDM [39, 40].

But, nested case–control studies, investigating resistin levels in early pregnancy, found no differences in resistin levels between GDM and controls (adjusted for BMI) [41]. Currently, there is no solid evidence that resistin is involved in the pathophysiology or prediction of GDM.

5.6 Omentin

Omentin-1, is an adipokine produced in non-fat cells from the adipose tissues (stromal vascular cells). It is involved in vascular tone relaxation due to the production of endothelial nitric oxide and lowering of both hs-CRP and TNFα signaling [42]. Omentin-1 was lower at the 2nd trimester of GDM similar to adiponectin, and in contrast to IL-6 [43].

5.7 Ghrelin

Hungarian study reported that fasting serum ghrelin levels were lower in women with GDM compared to non-pregnant healthy controls and pregnant controls without GDM in the 1st trimester and 3rd trimester [44].

6. Inflammatory markers

6.1 TNFα

TNFα a proinflammatory cytokine produced by monocytes and macrophages affects insulin sensitivity and secretion. These occurs from impairment of B-cell function and insulin signaling and results in insulin resistance and possibly GDM [45]. Multiple studies showed increased maternal TNFα levels in GDM, predominantly during late pregnancy [46]. Increased TNF-α levels in GDM than controls have been shown. Subgroup analysis detected this relationship to remain significant when they are compared with BMI-matched controls [47].

These increased levels are due to increased oxidative stress and inflammation arising from impaired glucose metabolism [48]. A small case–control study 0f 14 cases and 14 controls to address the predictive value of TNFα found no differences between women with GDM and without [49]. In one study of GDM and controls, TNFα levels measured pre-gravid, at 12–14 weeks and 34–36 weeks were increased at 34–36 weeks of gestation. These were inversely correlated with the insulin sensitivity [50]. We need more prospective studies to assess the predictive value of TNFα during GDM, with due adjustment for measures of adiposity.

6.2 Il-6

IL-6 is one of the proinflammatory cytokines and is increased in obesity and associated with indices of adiposity and insulin resistance, such as body mass index (BMI). The relationship between IL-6 and insulin action appears to be regulated via adiposity. However, in a case–control study, plasma IL-6 levels were elevated when adjusted for BMI in women with GDM [51].

6.3 High-sensitivity C-reactive protein (hsCRP)

Wolf and co-workers had found that the first-trimester CRP levels were significantly raised among them who later on developed GDM than the control subjects (3.1 vs. 2.1 mg/L, $P < 0.01$) [52]. After the adjustment for age, race/ethnicity, blood pressure smoking, parity, and age at gestation at CRP sampling, the increased risk of developing GDM among women was seen in the highest tertile than the lowest tertile and was 3.6 times higher (95% CI: 1.2–11.4). But when adjusted for BMI, this relation was not seen anymore. But Berggren and co-workers examined whether first-trimester hs CRP could predict the third-trimester impaired glucose tolerance (IGT). The hs CRP was positively correlated to (hs)CRP and GDM appears to be partly mediated by BMI.

Another study found that elevated plasma insulin and reduced adiponectin levels during first trimester may improve GDM identification rates than by clinical factors alone [53]. Maternal risk factors alone offer a prediction rate of 61% for GDM, but addition of adiponectin and SHBG, improved detection rates to 74% [54].

7. Glycaemic markers

7.1 Serum insulin and C-peptide

O'Malley E G et al. found that, both the serum insulin and C-peptide levels in the third tertile were correlated with GDM development ($p < 0.001$ if adjusted for

maternal obesity). Higher values of ghrelin were showing a lower odd of development of GDM, even after adjustment for maternal obesity. The conclusion of the study was though 3 of the 10 biomarkers were statistically indicating an increased risk of GDM, but the presence of large overlap in values between women with normal and abnormal glucose tolerance reflect that the biomarkers (alone or in combination) were not clinically helpfull [55].

7.2 Glucagon and PAI-1

Two small studies of 54 and 51 women reported higher levels of glucagon and PAI-1 respectively in women with GDM [56, 57].

8. Serum lipids

Li et al. compared 379 women in the first trimester who developed GDM subsequently with 2166 healthy women. They found that lipid profile was different between the groups. The GDM patients had higher concentrations of Triglyceride, LDL-Cholesterol and total cholesterol but lower concentrations of HDL [58]. The lipid values at first trimester in the cohort of Correa et al. was altered even when glycaemia and glycated hemoglobin were normal. The first trimester insulin concentration was seen to be also higher in women who developed GDM. Both theses indicate that there is a role of lipid metabolism in the pathogenesis of the disease [59].

9. Placenta-related factors

Placenta-Related Factors such as sex hormone-binding globulin, afamin, fetuin-A, fibroblast growth factors-21/23, ficolin-3 and follistatin, or specific micro- RNAs may be involved in GDM progression and may help in its recognition [60].

In GDM, some adipose-derived factors such as TNFα, visfatin, omentin and FABP4 may be also expressed and expressed from placenta, resulting to their elevated plasma levels [10]. The sex hormone binding globulin (SHBG) from placenta acting as a regulator of sex steroid hormones had been linked with inversely insulin resistance, metabolic syndrome, obesity and T2DM [61]. A lower level of plasma SHBG in the 1st trimester was a true biomarker for GDM [62, 63].

Nanda et al. showed reduced SHBG in parallel to adiponectin in GDM during 11–13th week of pregnancy, in presence of previous macrosomia, BMI > 30 kg/m2, and family history of DM [63, 64]. Similarly, an hepatokine promoter of insulin resistance, known as fetuin-B, is raised at the 3rd trimester of GDM, but returns after delivery [65]. Again, at the late 1st trimester, a reduction of plasma fetuin-A levels (and elevated hs-CRP) is also noted [66].

FGF-21, responsible for browning of white adipose tissue and an upstream effector of adiponectin, was increased in GDM at the 24th week of gestation [67]. Afamin, a glycoprotein member of the albumin family found in liver and placenta, may be a first trimester biomarker for pathological glucose and lipid metabolism [68].

The decreased levels of ficolin-3 (an activator of the lectin pathway of the complement system expressed in liver and placenta) and the increased ratio of ficolin-3/adiponectin are predictive of GDM at the 16–18th week of gestation [18]. Follistatin, a gonadal regulator of follicular-stimulant hormone and activin-A, having angiogenic, anti-inflammatory and cardioprotective properties, were lower in the 3rd trimester of GDM pregnancy [69].

The non-coding RNAs such as micro-RNAs (miR) can be released from placenta to maternal circulation as early as the 6th week of gestation and may be involved in placenta development, insulin signaling and cardiovascular homeostasis [70]. These miR can regulate trophoblasts proliferation, apoptosis, migration and invasion, and angiogenesis [71].

A significant downregulation of miR-29a, miR-132 and miR-222 had been reported in plasma at the 16th week of pregnant women who developed GDM [72]. Similarly, during the 7th–23rd week of gestation, elevated plasma levels of miR-21-3p were seen with GDM [73].

9.1 Sex hormone-binding globulin (SHBG)

SHBG a glycoprotein regulates the transport of sex hormones. In vitro, this is a marker in insulin resistance as insulin and insulin-like growth factor inhibit SHBG secretion. Indeed, a relation of low levels of SHBG and T2DM has been observed [74]. A study found its concentrations to be significantly lower in GDM [75]. Moreover, women treated with insulin showed even lower SHBG levels. Probably SHBG may help to differentiate or predict who will require insulin therapy or not.

A prospective study evaluated several biomarkers before 15 weeks of gestation and observed that low levels of SHBG were indicating an increased risk of GDM. Adding hs-CRP increases the specificity to 75.46% [76]. However another prospective cross-sectional study, revealed that low levels of SHBG assessed between 13 and 16 weeks of gestation were positively associated with the development of GDM ($n = 30$) ($P < 0.01$) [77]. A case–control study also found that SHBG in the non-fasting state in first trimester had a consistent association with an increased GDM risk [78].

10. Other potential biomarkers

AFABP or Adipocyte fatty acid-binding protein may be one of the risk predictors for cardiovascular disease, metabolic syndrome and T2DM [79]. Two studies have established its increased levels in GDM. Gestational diabetes mellitus causes changes in the concentrations of adipocyte fatty acid-binding protein and other adipo-cytokines in cord blood [80, 81]. Studies investigating the predictive value of AFABP in GDM have not been performed to date, however.

The fatty acid-binding protein 4 (FABP4) correlates with obesity markers e.g., fat mass and high BMI. FABP4 act on lipid and glucose metabolism via fatty acid transport and uptake [82]. The retinol-binding protein 4 (RBP4) is one of the circulating retinol transporters and id correlated with cardiometabolic markers in inflammatory chronic diseases like T2DM, metabolic syndrome obesity, and atherosclerosis process [83]. Higher levels of FABP4 can predict GDM from the 1st and 3rd trimester of [84, 85]. Upregulated values of plasma RBP4 in the 1st and 2nd trimester may modestly indicate GDM risk, especially among women with obesity and advanced age [18, 86].

10.1 Molecular biomarkers

Growing evidence suggests the use of SNPs, DNA methylation, and miRNAs as biomarkers that could help in the early detection of GDM. In presence of their potential, these molecular biomarkers pose several challenges that need to be addressed before they can become clinically applicable [87].

Decreased levels of first trimester pregnancy-associated plasma protein A (PAPP-A) and increased levels of second trimester unconjugated estriol (uE3) and dimeric inhibin A (INH) were associated with GDM [88].

10.2 Vitamin D

Lower levels of vitamin D have been seen in both obesity and type 2 diabetes and also in pregnancy very often. Low levels of Vitamin D levels during first trimester also carry a higher risk for GDM as seen in recent meta-analyses [89]. As the mentioned studies all were not randomized controlled studies, we need future RCTs to confirm the predictive role of vitamin D [90].

10.3 Candidate proteins

Zhao et al. studied maternal blood prospectively from pregnant women at 12–16 weeks of pregnancy. Among these, 30 women were subsequently diagnosed with GDM at 24 to 28 weeks and were selected as case studies along with 30 normoglycemic women as controls. They found that, four proteins, apolipoprotein E, coagulation factor IX, fibrinogen alpha chain, and insulin-like growth factor-binding protein 5, with a high sensitivity and specificity, may provide effective early screening for GDM. The panel of four candidate proteins could distinguish women subsequently developed with GDM from controls with high sensitivity and specificity [91].

10.4 Genetic markers

For the first time, Ding M et al. detected 8 variants to be associated with GDM, They are rs7957197 (HNF1A), rs3802177 (SLC30A8), rs10814916 (GLIS3), rs34872471 (TCF7L2), rs9379084 (RREB1), rs7903146 (TCF7L2), rs11787792 (GPSM1) and also rs7041847 (GLIS3). They also confirmed 3 other variants e.g., rs1387153 (MTNR1B), rs10830963 (MTNR1B), and rs4506565 (TCF7L2), which had been earlier identified by them or significant association with GDM risk [92].

10.5 Urine biomarkers

The study of urine metabolome profile in GDM during the 3rd trimester found relation of 14 metabolites with the steroid hormone biosynthesis and tryptophan metabolism, which were significantly high. They are l-urobilinogen, l-tryptophan, 21-deoxycortisol, cucurbitacin-C, ceramide (d18:0/23:0) and aspartame [93]. Upregulation of these pathways could aggravate insulin resistance and respond to oxidative stress and inflammation during GDM. Earliest at 12th–26th week of pregnancy, augmented levels of AHBA, 3-hydroxybutanoic acid (BHBA), valine, alanine, serotonin and related metabolites like l-tryptophan levels were observed in urine (and plasma) from GDM mothers [94].

11. Clinical prediction models incorporating biomarkers

Clinical risk prediction models' wave has been investigated in GDM. For example, the development of GDM can be predicted from the ethnicity, family history, history of GDM and body mass index. One large prospective study (n = 7929), found that, based on BMI, ethnicity, family history of diabetes and past history of GDM, there was a sensitivity, specificity and AUC of 73% [66–79], 81% [80–82]

and 0.824 (0.793–0.855), respectively, for the identification of GDM patients who required insulin therapy [95].

The introduction of biomarkers if added to a set of clinical risk factors are supposed to increase the predication rates of GDM. In particular, low HDL cholesterol and tissue plasminogen activator (t-PA) appeared as independent significant predictors of GDM. The addition of these 2 biomarkers to a group of clinical and demographic risk factors enhances the ROC (area under the curve) from 0.824 to 0.861 [96]. The t-PA not only is a predictor of GDM, it is also associated with a higher risk of T2DM [97].

Addition of maternal adiponectin and visfatin to a bunch of maternal risk factors, reached a detection rate of 68% [98]. The clinical implementation of these multi-parametric prediction models is determined by factors like practical acceptability, significant reduction in adverse pregnancy outcomes and cost-effectiveness. But these models need prospective validation studies and also further identification of predictive threshold values for the said biomarkers.

12. Metabolomic profiling

In one study, women with GDM (n = 96) were matched to women with NGT (n = 96) by age, BMI, gravidity and parity and the levels of 91 metabolites measured. Six metabolites (anthranilic acid, alanine, glutamate, creatinine, allantoin and serine) were found to have significantly different levels between the two groups in conditional logistic regression analyses ($p < 0.05$). Metabolic markers identified as being predictive of type 2 diabetes may not have the same predictive power for GDM [99].

Endogenous galanin as a novel biomarker to predict gestational diabetes mellitus is also observed [100]. The higher level of galanin observed in GDM may represent an adaptation to the rise of glucose, weight, GGT associated with GDMs thriving for clinically useful thresholds [101].

Mean 1,5 AG levels are significantly lower in those that go on to develop GDM. Hs-CRP and SHBG are important early predictors of GDM. Adding SHBG to hs-CRP improves specificity and serves good overall accuracy. Uric acid, creatinine and albumin have no role in GDM prediction [102].

Bivariate logistic regression analysis had shown that both adiponectin and insulin highlight future development of gestational diabetes. Both of them measured at 11 weeks, may predict oncoming GDM. But we need further studies to assess the reliability of these biomarkers [103].

Placental growth factor (PLGF), a vascular endothelial growth factor-like protein, is highly expressed in the placenta. About three studies suggest that higher early pregnancy PLGF levels are associated with GDM [104–106]. Recently, ALT, a liver enzyme, a marker of hepatocellular damage, has been examined as a first-trimester predictor of GDM [107].

One moderate-sized study (N = 182) showed that glycosylated fibronectin measured in the first trimester could predict GDM with high accuracy [108]. Watanabe et al. assessed the soluble (pro)renin receptor levels in 716 Japanese women at less than 14 weeks of gestation and found increased levels in women who developed subsequent GDM [109]. In a case–control study of 1000 women from the UK, Syngelaki et al. found that maternal serum TNF-alpha measured at 11–13 weeks gestation was associated with subsequent GDM [110].

Donovan et al. in their study, indicated that women diagnosed with GDM have lower first trimester levels of both pregnancies associated free β-hCG and plasma protein-A (PAPP-A) than normoglycemic pregnant women. These two markers may

indicate the presence of abnormal glucose metabolism at the beginning of pregnancy and may help for identification of future development of GDM [111].

13. First trimester biomarkers for prediction of gestational diabetes mellitus

Tenenbaum-Gavish et al. in a cohort of GDM group found that, compared to the normal group BMI and insulin (P = 0.003) were higher (both P < 0.003). The soluble (s)CD163 and multiples of median values of uterine artery pulsatility index (UtAPI) were high (p for both <0.01) but, pregnancy associated plasma protein A, tumor-necrosis factor alpha and placental protein 130, were low (p for all <0.005). There was no significant difference between the groups in placental growth factor, leptin, interleukin 6, soluble mannose receptor or peptide YY. For screening GDM in obese pregnancy a combination of high BMI, TNFα, insulin and sCD163 reached an AUC of 0.95, and the detection rate of 89% with a 10% false positive rate. For nonobese pregnancy, the combination of TNFα, PP13,sCD163 and PAPP-A showed an AUC of 0.94 and the detection rate was 83% at 10% false positive rate [112].

14. Conclusion

By blood sugar estimation when GDM is diagnosed, adverse foetal changes have already set in. So, we will have to attempt to diagnose GDM, before the foetal changes take place. It would be more rewarding if we can diagnose impending GDM and alert the person even when she plans for pregnancy.

Different biomarkers e.g., glycemic, insulin resistance, inflammatory, adipocyte and placenta-derived, had been evaluated as the first-trimester predictors of GDM. The majority of these studies are smaller in size and was based on case–control designs. But some large studies of glycemic markers indicated that hemoglobin A1C and/or fasting glucose help in detecting women without diagnosis of previous diabetes and they may be benefited from early detection and treatment of GDM, though these observations should be confirmed by interventional studies.

The improvement of GDM development and outcomes is possible by earlier and more specific identification of GDM accompanied by metabolic and cardiovascular risks. In line with these, first or second trimester-related biomarkers seen in maternal plasma like adipose tissue-derived factors like adiponectin, omentin-1, visfatin, fatty retinol binding-protein-4 and acid-binding protein-4 reflect correlations with development of GDM. In addition, placenta-related factors e.g., sex hormone-binding globulin, afamin, fetuin-A, ficolin-3 and follistatin, fibroblast growth factors-21/23 and specific micro-RNAs may be important in detecting progression of GDM and its recognition. Finally, urinary metabolites related to non-polar amino-acids and ketone bodies, serotonin system, may help in completing a predictive or early diagnostic group of GDM biomarkers.

To transform the observations obtained from observational studies into clinical practice, we need also more clinical trials or cost-effectiveness analyses of screening and treatment c.onsidering the first-trimester biochemical GDM predictors. Further studies should examine the first-trimester biochemical markers for adverse outcomes in GDM by prospective trials to find its prevention or early treatment.

GDM involves a significant proportion of pregnant women and is becoming more prevalent as rates of obesity rise globally. Its development and complications could be arrested if accurately predicted in early pregnancy even if possible before conception and effective interventions initiated. Many Several biomarkers have

been studied to understand pathogenesis of GDM, but till date none are showing adequate robustness to be used for clinical algorithms for prediction of GDM.

Application of the high methodologies gives novel insights about the role of genetic variants, metabolomics and epigenetics regarding the pathogenesis of GDM. This option for using a predictive model during the subclinical phase of GDM appears to be promising as an important arena of future research and development. These modern technologies are off course complex and not applicable to mass level screening. There are also issues related to validity across populations, reproducibility, and selectivity. We will have to find out methods with cost-effectiveness and universal access, otherwise the present complex biomarkers are likely to prove invaluable in the diagnosis of GDM.

The emerging evidences suggest that the assessment at eleven and thirteen weeks of gestation, should be the platform towards a new approach in antenatal care. The data from the maternal history should be added to the results of biochemical and biophysical tests to examine the patient-specific risk related to a wide variety of pregnancy complications. Ideal GDM biomarkers appears to be a combination of several molecular biomarkers to balance the lack of sensitivity and specificity of individual factors. But targeted rapid technological advances will overcome these challenges and develop a quick, cost-effective point-of-care test that can accurately identify women at high risk for GDM during early pregnancy even if before conception.

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