Received: 4 April 2025 | Revised: 22 July 2025 | Accepted: 4 August 2025

DOI: 10.1111/aogs.70046

AOGS Acta Obstetricia et Gynecologica Scandinavica

STATE-OF-THE-ART REVIEW

First-trimester biomarkers of gestational diabetes mellitus: A scoping review

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Abstract

Gestational diabetes mellitus (GDM) affects approximately 14% of pregnancies globally, with rising incidence depending on the diagnostic criteria used. In the UK, screening relies on risk factors at booking, followed by a diagnosis via an oral glucose tolerance test in the second trimester. This approach may lack sensitivity and has poor tolerability. Emerging evidence suggests that GDM pathophysiology begins in the first trimester, with biomarkers showing potential for early prediction. Identifying these could enable earlier risk stratification, improved diagnostic pathways, and better maternal–fetal outcomes. This scoping review maps the existing literature on first-trimester biomarkers of GDM to evaluate their clinical utility and integration into predictive models. A literature search was conducted using Medline, Embase, and PubMed to identify studies on first-trimester biomarkers of GDM. Inclusion criteria included (1) studies investigating biomarkers at <15 weeks' gestation; (2) studies that diagnosed GDM using an OGTT with recognized diagnostic guidelines or clearly stated glucose thresholds. A total of 133 studies were included, reporting a wide range of biomarkers (145 in total). PAPP-A was generally lower in GDM, with mixed findings for β-hCG and PlGF. Metabolic markers, including lipid profiles, fasting glucose, and HbA1c, were often elevated. Inflammatory markers, such as WCC, neutrophils, and CRP, were higher in those later diagnosed with GDM. First-trimester biomarkers highlight GDM's complex pathophysiology. PAPP-A shows predictive potential, while metabolic and inflammatory biomarkers suggest early systemic dysfunction. Emerging tools like 3D ultrasonography indicate placental structural changes. Larger studies are needed to validate these biomarkers and integrate them into predictive models to improve maternal–fetal outcomes.

KEYWORDS
first biomarkers PAPP-A (pregnancy-associated plasma protein-a) PlGF (placental growth factor) inflammatory markers insulin resistance, gestational diabetes mellitus pregnancy trimester

Abbreviations: GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PAPP-A, plasma associated protein A; PlGF, placental growth factor; β-hCG, beta-human chorionic gonadotrophin; TG, triglycerides; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; CRP, C-reactive protein; FT3, free triiodothyronine; FT4, free thyroxine.

1 | INTRODUCTION

Gestational diabetes mellitus (GDM), defined as hyperglycemia or glucose intolerance with onset or first recognition during pregnancy, is one of the most common conditions in pregnancy. It is associated with adverse perinatal outcomes including increased odds of cesarean section, a large for gestational age infant, and admission to the neonatal intensive care unit.[1] Global prevalence of GDM is estimated at 14%,[2] with incidence rising along with increasing rates of obesity and prediabetes in premenopausal women.[3,4]

In the UK, screening for GDM is not universal but instead relies on a risk factor-based approach at the time of pregnancy booking, typically at less than 10 weeks' gestation. Women are offered testing for GDM if one or more of the following risk factors are present: BMI above 30, previous macrosomic baby (BW ≥4.5 kg), previous gestational diabetes, family history (first degree relative) with diabetes, an ethnicity with a high prevalence of diabetes.[5] The primary diagnostic test for GDM remains the 75 g 2-h oral glucose tolerance test (OGTT), typically performed at 24–28 weeks' gestation or earlier from 16 weeks if higher risk factors are present. Diagnosis is confirmed if the fasting plasma glucose level is ≥5.6 mmol/L or the 2-h plasma glucose level is ≥7.8 mmol/L.[5] Despite its widespread use, the OGTT has several limitations. The test involves an overnight fast followed by drinking a glucose solution with subsequent blood glucose testing. This is poorly tolerated by many women, with side effects such as nausea and vomiting being the most common reason for non-completion at 16.5%.[6] The UK National Screening Committee reviewed the evidence for universal screening in 2021 and does not currently recommend it, citing the lack of an alternative validated screening test for GDM.[7] These challenges highlight the need for a more accessible and reliable method for early identification of women at risk of GDM.

Since the introduction of aneuploidy and preeclampsia screening in the first trimester, there has been increasing research to identify how these are affected in GDM. A large systematic review and meta-analysis by Donovan et al.[8] highlighted that lower levels of both pregnancy association plasma protein-A (PAPP-A) and free beta-human chorionic gonadotropin (β-hCG) are associated with an increased risk of GDM later in pregnancy. This emerging evidence shows that the pathophysiological changes that cause GDM occur long before a clinical diagnosis is made, with these being detected in the early stages of pregnancy before the typical screening window at 24–28 weeks. This has led to a growing interest in identifying first-trimester biomarkers that could either predict or risk stratify for GDM. By detecting GDM earlier, it would allow earlier interventions, either through diet and lifestyle or pharmacological, which could improve maternal–fetal outcomes. This is supported by the findings of the RADIEL study, which found that lifestyle intervention during pregnancy and the first postpartum year was effective in preventing GDM and postpartum glycemic abnormalities, particularly among women at the highest genetic risk of type 2 diabetes.[9]

The aim of this scoping review is to summarize the existing literature on the range and utility of first-trimester biomarkers in the prediction of patients at high risk of developing GDM.

Key message

This review identifies diverse biochemical and placental first-trimester biomarkers of GDM, highlighting that pathology precedes second trimester diagnosis. Findings support developing early diagnostic strategies in the first trimester to guide timely interventions and reduce adverse outcomes.

2 | MATERIAL AND METHODS

2.1 | Eligibility criteria, information sources, and search strategy

A literature search was conducted in December 2024 using Medline (via Ovid), Embase, and PubMed to identify studies on associations between maternal biomarkers and GDM in the first trimester. The following search terms were used: ("Gestational Diabetes" OR "Gestational Diabetes Mellitus" OR "GDM" OR "Pregnancy Induced Diabetes") AND ("Biomarker*" OR "Predictor*" OR "marker" OR "Biological marker" OR "Placenta*" OR "Placenta Growth Factor" OR "PlGF" OR "Pregnancy Associated Plasma Protein A" OR "PAPP-A") AND ("First trimester" OR "Pregnancy Trimester, First" OR "Early Pregnancy" OR "early gestation" OR "0–14 weeks gestation" OR "up to 14 weeks gestation"). The full search strategy is outlined in Table S1. No restrictions were placed on publication year to capture all relevant studies. Only observational studies involving humans were excluded. Articles that were not published in English were excluded during the abstract and full-text screening. Reviews were excluded but used for reference mining. The systematic search was performed in line with and validated by University of Oxford's Bodleian Library.

2.2 | Inclusion and Exclusion Criteria

Inclusion criteria included (1) studies investigating the association of a biomarker with GDM at <15 weeks' gestation; (2) studies that diagnosed GDM using an OGTT with any recognized or referenced diagnostic guideline or clearly stated glucose levels from the second trimester. Full inclusion and exclusion criteria are outlined in Table 1.

2.3 | Article Selection

Duplicated articles were removed using the Zotero duplicate function by MS. Articles were then screened by title and abstract to exclude irrelevant studies. If the abstract mentioned GDM as an outcome and first trimester, or related early pregnancy terms,

TABLE 1 Full inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Studies involving pregnant women at <15 + 0 weeks gestation of any age, ethnicity or location	Studies involving gestation >15 weeks and preexisting diabetes
Studies investigating any potential biomarker of GDM – blood-based (PlGF, PAPP-A), genetic, inflammatory, placental markers (volume and vascularity)	Studies that do not clearly define GDM using established diagnostic criteria or that focus on conditions unrelated to GDM
Studies that explicitly report GDM as an outcome	Editorials, letters, commentaries, reviews (except systematic reviews for reference mining), conference abstracts without full data
Studies that use an oral glucose tolerance test to diagnose GDM with either recognized or clearly stated diagnostic criteria from the second trimester	Studies using methods other than OGTT to diagnose GDM, that is, Hemoglobin A1c (HbA1c)
Observational studies, such as, cohort studies, case-control studies, and nested case-control studies, that provide data on biomarkers assessed during the first trimester	Studies involving animals or in vitro experiments, or that primarily focus on nonpregnant populations Studies where *N*: <10

the article was included for full-text review. Two investigators (MS and SK) independently reviewed all articles by full text against the inclusion and exclusion criteria. Disagreements were discussed and resolved with a third investigator (SM).

2.4 | Data Extraction

Included articles were exported into an Excel template for data extraction on publication year and country, study type and design, selection criteria, biomarkers and the gestation researched at, case numbers, GDM diagnostic criteria, methods, and gestation.

2.5 | Data Synthesis

During the study selection process, the large number of studies identified, wide range of biomarkers examined, and variation in GDM diagnostic criteria became evident. This posed challenges for data synthesis and direct comparisons between studies. Due to this, a meta-analysis was not performed; pooling the data would not have been possible. Instead, a narrative synthesis was conducted to summarize key characteristics of the studies identified. This approach has provided a broad insight into the current literature on first-trimester biomarkers of GDM, and despite the absence of quantitative data aggregation, has allowed us to identify gaps in the research for possible future studies.

3 | RESULTS

3.1 | Study identification

A total of 2015 articles were identified through the literature search. A total 819 duplicates were excluded using the Zotero duplicate function. After screening by title and abstract, 336 articles were included for full-text screening. Of these, 203 papers were excluded, and 133 met the inclusion/exclusion criteria and are reported in the PRISMA flow diagram; see Figure 1.

3.2 | Study Characteristics

The included 133 studies were conducted in 31 countries and published from 2003 to 2024. The majority of studies originated in China (49 of the 133 included studies); a breakdown of the country of origin is provided in the supporting information; see Figure S1. There were 58 retrospective studies and 75 prospective studies, with 111 from single institutions and 23 multicentric. GDM cases ranged from 10 to 4669, totaling 114 227 and 189 563 non-GDM cases. The total number of participants across all studies was 303 790. A table summarizing all study characteristics is included in the supporting information; see Table S2.

About 145 distinct biomarkers were identified, with the most common individual biomarker being PAPP-A and the most common group being lipid profile. GDM diagnostic criteria ranged widely, with the most common guideline used being the International Association of the Diabetes and Pregnancy Study Groups. A full outline of diagnostic criteria used is included in supporting information; see Tables S3a and S3b. Biomarkers were categorized into either blood-based, routine or nonroutine, ultrasound, maternal, or novel. The most commonly examined biomarkers were routine blood-based; see Table 2. A further outline of the individual biomarkers within these categories is included in the supporting information; see Table S4, and their frequency; Figure S2.

A full table with results from the data extraction of studies outlined below is included in supporting information; see Table S5.

3.3 | Quality assessment

A formal quality assessment of the included studies was not undertaken; the aim of this scoping review was to map the wide range of biomarkers in the existing literature, rather than to evaluate the strength of existing studies.

3.4 | PAPP-A

Of the 21 studies that looked at the association between first trimester PAPP-A and GDM, 16 found levels to be lower in GDM,[10–25] and 5 found no difference.[26–30]

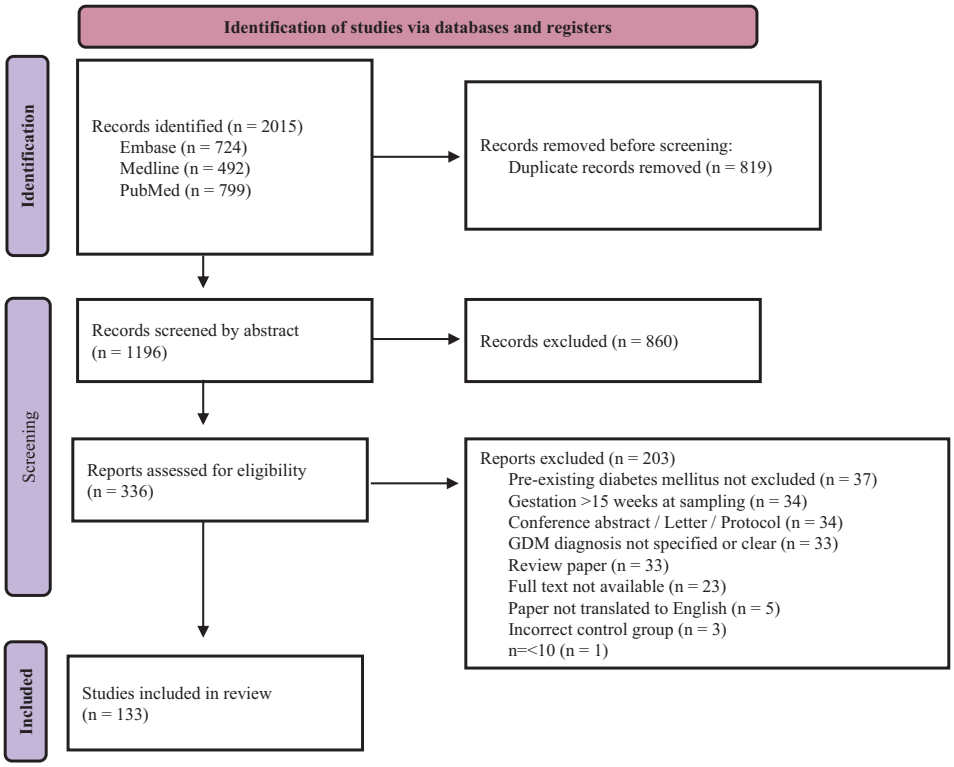

FIGURE 1 Flowchart of study selection process.

TABLE 2 Number of biomarkers identified by category.

Individual biomarkers identified	145
Blood-based markers (routine)	54
Blood-based markers (nonroutine)	49
Ultrasound markers	22
Maternal characteristics	5
Novel markers	26

3.5 | β-hCG

A total of 17 studies investigated β-hCG as a biomarker for GDM, with 13 finding no difference[12–15,18,19,21,22,24,26,27,29–30] and three showing lower β-hCG in patients diagnosed with GDM.[11,16–17] One study looked at the association between glucose levels and β-hCG.[31]

3.6 | Placental Growth Factor

Of the five papers that look at the association of PlGF and GDM, three found PlGF to be higher in GDM[20,29,32]; one found lower levels[12] and another found no difference.[33]

3.7 | Ultrasound Markers

Two included studies have investigated placental sonographic markers in the first trimester with GDM.[34,35] Wong et al. found only Vascularization Index (VI) and Vascularization Flow Index (VFI) to be statistically lower in GDM, with no difference in placental volume (PV) or Flow Index (FI).[34] Han et al. found that PV, as well as VI and VFI, were significantly smaller in the GDM group, with no difference found in FI. The diagnostic potential of these was also commented on, with VFI returning the largest AUC of 0.73, with sensitivity and specificity of 60.00% and 80.19%, respectively. When combining PV and VFI with maternal age and gravida, the regression model indicated a higher accuracy for GDM prediction.[35]

Other ultrasound biomarkers investigated include uterine artery pulsatility index (UtAPI) and nuchal translucency (NT). Four studies investigated UtAPI, with two finding this to be lower in GDM[14,18] and two finding no difference.[12,34] Ten studies investigated the association of NT and GDM, and all found no difference.[15,17,21,22,26,27,29,30,35–36]

3.8 | Lipid profile

In total, 27 studies investigated various biomarkers as part of lipid profile in the first trimester, including total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), TG/HDL ratio, LDL/HDL ratio, and triglyceride glucose index (TyG). Of the 19 studies that investigated TC, 13 found higher levels[16,23,37–47] and six did not find any association.[48–53] Of the 21 studies that investigated triglyceride, 14 studies found TG to be higher in GDM,[16,23,37,38,40–43,45,46,52–55] whereas six found no difference,[39,44,48–51] and one study found TG lower.[56]

Of the 16 studies investigating LDL, 10 found it to be higher in GDM,[16,23,37–40,42,44,46,52] five found no difference[41,49–51,53] and one found LDL to be lower.[45] Seventeen studies investigated HDL, of which 13 found no significant association,[23,37,38,40–42,44,49–53] two found HDL to be higher in GDM,[45,46] and two found HDL to be lower.[16,54] Five studies looked at TG/HDL ratio, with four finding this to be elevated in GDM[43,45,53,55] and one finding no difference.[39] Two studies investigated LDL/HDL ratio in GDM, and of these, one found this to be higher[43] and one found no association.[55] One study investigated TyG index and found this higher in GDM.[55]

3.9 | HbA1c

Seventeen studies were identified that investigated first-trimester HbA1c. Eleven studies found higher HbA1c levels were associated with later diagnosis of GDM.[33,41,42,44,57–63] Three studies commented on HbA1c cut off values and found that HbA1c levels of >5.7%,[64] >5.33%[65] and >5.35%[66] were all associated with higher odds of developing GDM. One study did not find any significant association between HbA1c and GDM.[40]

3.10 | Liver function tests

Seven studies investigated the association of various biomarkers associated with liver function tests (LFTs). Five studies investigated alanine aminotransferase (ALT) with three finding no significant association[40,53,57] and two finding higher levels in GDM.[67,68] Five studies looked at aspartate aminotransferase (AST) with four studies finding no difference[40,53,57,68] and one finding AST to be higher in GDM.[67] Four studies investigated gamma-glutamyl transferase (GGT) with three studies finding higher levels in GDM[57,67–68] and one finding no difference.[53] Two studies investigated alkaline phosphatase (ALP) with one finding it to be higher in GDM[68] and one finding no difference.[40] One study also found no difference in bilirubin levels but increased levels of both globulin and albumin, with overall significantly higher levels of abnormal first-trimester LFTs.[68]

3.11 | Markers of insulin resistance

We identified 27 studies investigating a range of biomarkers associated with insulin resistance. Twenty studies investigated fasting plasma glucose, with 17 finding this is higher in GDM[10,38,45,51,55–57,59,60,62,69–75]; and three finding no difference.[47,76–77] Two studies also investigated 1- and 2-h plasma glucose levels, with both finding these to be higher in GDM.[59,62] Seven studies investigated fasting plasma insulin, with four studies finding this to be increased[40,47,75,78] and three finding no difference.[51,74,76] Seven studies investigated adiponectin, with five studies finding lower levels in GDM and three studies finding no difference.[40,48,79] Five studies investigated the role of leptin, and of these, three found leptin to be higher in GDM[79–81] and two found no difference.[40,78] One study found C-peptide to be higher in GDM.[75] Six studies investigated the role of Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) with four finding it to be elevated in GDM[40,47,51,75] and two finding no difference.[74,76] One study found Irisin to be lower in GDM.[76] Two studies investigated Resistin, with one finding levels to be higher in GDM[81] and one finding no difference.[78]

3.12 | Inflammatory markers

Ten studies investigated the association of inflammatory markers with GDM, including C-Reactive Protein (CRP), high-sensitivity C-reactive protein (hs-CRP), TNF-alpha, and Interleukin-6 (IL6). Of the three studies that looked at CRP, two found CRP to be higher in patients with GDM[82,83] and one found no difference.[70] One commented on cut off values for CRP, finding that levels >5.3 g/L were associated with an increased risk of GDM.[83] Six studies specifically investigated hs-CRP, with six finding it to be elevated in GDM[46,48,74,84] and two finding no difference.[85,86] One study found that TNF-alpha is higher in patients with GDM.[86] Another study found that IL6 is higher in patients with GDM.[87]

3.13 | Hematological markers

Eleven studies investigated a range of hematological markers. Eight studies investigated hemoglobin (Hb) with four finding first-trimester Hb to be higher in GDM[23,44,59,88] and four finding no significant difference.[41,60,89–90] Three studies investigated neutrophil count, and all found that this is significantly elevated in patients who subsequently develop GDM.[23,91–92] Three studies investigated lymphocyte count, with two finding this to be higher in GDM[23,92] and one finding no difference.[91] Four studies investigated platelet count, with three finding no association with GDM[90–92] and one finding it to be elevated.[23] Three studies investigated white blood cell count (WBC) and all found this to be significantly elevated in GDM.[23,91–92] Two studies investigated monocyte count, with one finding this to be elevated[92] and one finding it to be decreased in GDM.[91] One study investigated monocyte lymphocyte ratio (MLR) and found this to be lower in GDM.[91] Three studies investigated neutrophil lymphocyte ratio (NLR) and all found higher levels in GDM.[23,91–92] Two studies investigated mean cell volume (MCV) with one finding it to be lower[60] and one finding no difference.[59] Two studies investigated mean platelet volume (MPV) with one finding it to be higher in GDM[90] and one finding no difference.[23] One study investigated coagulation markers, finding that PT, INR, and APTT were decreased in GDM, and fibrinogen and D Dimer were increased.[93]

3.14 | Thyroid Function Tests

Six studies investigated the association between thyroid function tests and GDM, focusing on free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH) and FT3/FT4 ratio. Of the three studies that investigated FT3, one found it to be statistically higher in GDM than controls[94] and the other two did not find any significant association.[41,95] Five studies investigated FT4, with three finding lower levels in GDM[94–96] and two finding no association.[41,42] Five studies investigated TSH, with four finding no significant association[41,42,94–95] and one finding elevated TSH in GDM.[96] FT3/FT4 ratio was investigated by two studies, with both finding elevated ratios in GDM.[94,95]

3.15 | Sex Hormones

Eleven studies investigated the association between various sex hormones. One study investigated progesterone and prolactin and found that they are both significantly lower in GDM.[97] Another study investigated testosterone and DHEA-S and found that testosterone is higher in GDM; but there is no difference in DHEA-S.[98] Nine studies investigated sex hormone-binding globulin (SHBG) and of these, seven found that SHBG is lower in GDM[42,47,48,63,85,99–100]; one found no difference,[40] and another found higher levels in GDM.[101]

3.16 | Ferritin

Three studies investigated the association between Ferritin and GDM. Two did not find any direct significant association[23,70]; the third found that pregnancies that later developed GDM had a significantly higher level of ferritin (>31.35 ng/mL).[82]

3.17 | Vitamin D

Three studies investigated the association between vitamin D and GDM. One study found a significant association between vitamin D insufficiency and GDM.[102] Two found no difference.[52,103]

3.18 | Novel Markers

A total of 26 studies investigated 27 different novel biomarkers, including micro and exosomal RNAs. Due to the wide range of markers examined, we were not able to group them for comparison. Although some show promise in small-scale studies, their clinical utility and inclusion into predictive models remain limited. As this scoping review focused on clinically applicable biomarkers, data was not extracted for novel and other molecular biomarkers.

4 | DISCUSSION

In this scoping review, we have demonstrated the range and breadth of potential first-trimester markers for GDM, and the heterogeneity of findings with respect to their predictive potential.

PAPP-A, produced by placental trophoblasts, has a key role in fetal growth. It is an established biomarker and is used clinically in first-trimester aneuploidy screening. Most studies in this scoping indicated that PAPP-A is lower in pregnancies that go on to develop GDM, supported by a systematic review by Donovan et al.[8] PAPP-A increases the bioavailability of insulin-like growth factor 1 (IGF-1), with lower levels therefore reducing IGF-1 activity, contributing to hyperinsulinemia by disrupting glucose metabolism. This underscores the potential utility of PAPP-A as a first-trimester biomarker of GDM.

β-hCG, mainly produced by placental syncytiotrophoblasts, peaks in the first trimester and plateaus in the second trimester until delivery. It has clinical uses in the evaluation of trophoblastic disease but also in the combined screening test for aneuploidy. The majority of the studies highlighted in this review did not show a significant difference in β-hCG levels; although the studies observing lower levels had larger sample sizes which could account for the wider variability in β-hCG levels.

PlGF is part of the vascular endothelial growth factor family and has pro-angiogenic effects on the fetal and placental circulations. While low PlGF is commonly associated with pre-eclampsia and fetal growth restriction, its role in GDM has been less researched. Most studies investigating first-trimester PlGF in GDM reported abnormal levels, with the majority of these indicating elevated levels. A systematic review of placental histopathology in maternal diabetes highlighted that the most common finding was increased villous immaturity and angiogenesis.[104] Higher levels of PlGF suggest abnormal placental angiogenesis, with these possibly reflecting the compensatory mechanisms aimed at enhancing placental blood flow to account for insulin resistance and optimize fetal nourishment. The observation of elevated PlGF levels in some studies indicates that this angiogenesis starts in the first trimester preceding a clinical diagnosis of GDM, underscoring the role of PlGF as an emerging first-trimester biomarker of GDM. However, further research is required to elucidate the underlying mechanism driving these vascular changes and the gestation at which they occur.

With the improvements in 3D ultrasonography, PV and vascularization indices are emerging as potential first-trimester biomarkers of clinical diseases, with roles in both fetal growth restriction and preeclampsia. Studies investigating this reported reduced vascular indices, linking the vascular changes seen at term with the first trimester.[34,35] This supports the hypothesis that hyperglycemia disrupts placental angiogenesis, leading to less efficient vasculature.[105] Both studies had small sample sizes, highlighting the need for a larger scale study to further investigate and validate these findings. Other ultrasound markers investigated included UtAPI and NT. No study found NT to differ between GDM and healthy controls,

suggesting its limited potential as a first-trimester biomarker of GDM. Interestingly, the two larger studies investigating UtAPI found it to be lower in GDM, correlating with the hypothesis that placental vascular changes are present in the first trimester of pregnancies subsequently diagnosed with GDM.

Studies investigating metabolic biomarkers consistently demonstrate a strong trend toward altered metabolism in GDM. Lipid profiles were predominantly higher in GDM cases, reflecting the known dyslipidemia associated with insulin resistance. The presence of these in the first trimester suggests that people with dyslipidemia have a predisposition to GDM, supporting the concept of lipid-induced insulin resistance.[106] Identifying abnormal lipid profiles in the first trimester could provide a window for lifestyle interventions to prevent GDM development.

Liver function tests showed subtler differences; and, although no studies found lower levels in GDM, most reported no difference. Notably, GGT was the only marker consistently higher, aligning with previous research.[107] Increased GGT reflects greater hepatic fat deposition, which is closely linked with insulin resistance, highlighting its potential as a GDM biomarker. While higher BMI is associated with both GDM and abnormal LFTs, it has been shown that these are independently associated with GDM, further supporting their potential as first-trimester biomarkers.[68]

Few studies investigated thyroid function tests, but all reported elevated FT4 levels. This is reflected in previous studies and reviews finding an inverse correlation between FT4 levels and risk of developing GDM.[108,109] Since hypothyroidism is linked with insulin resistance,[110] low first-trimester FT4 reflects the hypothesis that insulin resistance is present before GDM is diagnosed clinically, reinforcing this as a possible biomarker of GDM.

Given its association with long-term glycemic control, HbA1c has been widely explored as a potential marker of GDM. Almost all studies included in this review found HbA1c to be elevated in people diagnosed with GDM, suggesting that a degree of insulin resistance and impaired glucose tolerance exists prior to clinical diagnosis. However, despite HbA1c being elevated in patients diagnosed with GDM, the value of this was still within the normal range for nonpregnant patients. This highlights the need to investigate clinically relevant cut off values for first trimester prediction, as current thresholds may not capture the early glycemic dysregulation.

These metabolic biomarkers highlight a broader trend of endocrine and hepatic dysregulation present in GDM, reinforcing the hypothesis that the pathophysiology of GDM begins well before its diagnosis in the second trimester. The dysregulated pathways involved in GDM development can be seen as early as the first trimester, further highlighting a need to further investigate first-trimester biomarkers.

Multiple studies have demonstrated increased markers of oxidative stress and inflammation in GDM, with evidence suggesting that these extend as early as the first trimester.[111] This review similarly found a trend toward a pro-inflammatory state in the first trimester in people later diagnosed with GDM.

CRP is an acute phase protein linked to systemic inflammation, obesity, and insulin resistance, both being key risk factors for GDM. The majority of studies from this review reported elevated levels of CRP in GDM. Among the hematological markers, WCC and neutrophil count showed the strongest associations with GDM, both being significant markers of inflammation. These findings support the hypothesis that a low-grade pro-inflammatory state and oxidative stress are present in GDM as early as the first trimester, potentially driven by hyperglycemia secondary to preexisting insulin resistance.

Compared with other biomarkers, there has been less research into the association between sex hormones and GDM. Of the sex hormones, SHBG was the most frequently investigated and largely found to be lower in GDM. SHBG has been inversely linked to insulin resistance, with lower levels associated with a higher risk of Type 2 Diabetes Mellitus[112]; correlating with the trend observed in this review. This further underpins the underlying role of insulin resistance in the first trimester of patients who later develop GDM.

The main strength of this scoping review is the large number of studies included, encompassing a wide range of settings and populations due to the broad inclusion criteria. The narrative synthesis highlights emerging trends and offers valuable insight into the current research landscape. To the best of our knowledge, this is the first scoping review to map the existing literature on any first-trimester biomarker of GDM.

However, a key limitation is the lack of formal quality assessment. Given the large volume and heterogeneity in studies, individual quality and bias were not evaluated. The variation in biomarker types, diagnostic criteria, and study populations further limits comparability between studies. A meta-analysis would be required to assess the clinical utility and predictive potential of these biomarkers, which was not feasible within this review. Additionally, not all identified studies were discussed within the main text. To focus on the clinical utility of the biomarkers identified, only studies evaluating clinically applicable biomarkers were discussed. All identified studies from the search have been outlined within Table S1 with a reference list in Table S6 to ensure accessibility. We have also specifically not included first-trimester OGTTs given that they are not widely accepted for diagnosis or screening due to their limited specificity and low predictive value. A further limitation is the exclusion of gray literature, which was not feasible due to the large volume of articles retrieved. As a result, some unpublished relevant studies may have been missed.

While our initial literature search included up to 14 weeks gestations in the search terms, during the data analysis this was extended to include papers up to 15 + 0 weeks. This accounted for studies reporting "14 weeks" without specifying if this referred to 14 + 0- or 14 + 6-weeks' gestation. Another limitation is the variability in how gestational age was defined across studies, ranging from last menstrual period to ultrasound. Due to the volume and heterogeneity of studies, we relied on the gestational age provided by the authors and did not exclude on the basis of how this was decided. This may introduce variability in gestational age across studies.

Finally, a further limitation is that this scoping review was not registered a priori. Although this is not mandatory for scoping reviews, it would have strengthened our review process.

5 | CONCLUSION

This scoping review highlights the complexity of GDM with a wide range of first-trimester biomarkers involved in its pathophysiology. Our findings support a growing body of evidence that this pathology exists prior to diagnosis in the second trimester. With rising rates of GDM and its associated long-term cardiovascular and metabolic risks, the need for early interventions is increasingly important. This review underscores a clear unmet clinical need to shift the focus of GDM risk stratification toward the first trimester.

Advances in three-dimensional USS and power Doppler have enabled the use of placental volume and vascular indices as potential biomarkers of GDM. This has the possibility of integration within the first-trimester dating scan, along with established first-trimester biomarkers, such as PAPP-A and PlGF. Their accessibility and routine clinical use could allow for easy integration within a predictive model for GDM with little extra cost or clinical burden.

Given the increasing prevalence of GDM, future research should focus on validating first-trimester predictive models that combine history, demographics, and biomarkers with a view to integrate this into routine clinical practice. These models could not only help identify at-risk individuals but also allow earlier targeted interventions to mitigate the progression or severity of GDM and reduce associated adverse outcomes.

AUTHOR CONTRIBUTIONS

The literature search and systematic review were performed by May Swinburne. The data collection and analysis were performed by May Swinburne, Samuel Krasner, and Sam Mathewlynn. The writing of the manuscript was performed by May Swinburne, and Sally Collins oversaw the concept, method, analysis, and completion of the project.

ACKNOWLEDGMENTS

We acknowledge the support of the Nuffield Department of Women's and Reproductive Health at the University of Oxford for providing access to the resources and databases essential for this research. We are also grateful to the University of Oxford's Bodleian library in the assistance and validation of the systematic search strategy.

FUNDING INFORMATION

No funding was required for this review.

CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICS STATEMENT

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Swinburne M, Krasner S, Mathewlynn S, Collins S. First-trimester biomarkers of gestational diabetes mellitus: A scoping review. *Acta Obstet Gynecol Scand*. 2025;00:1-11. doi:10.1111/aogs.70046