HJOG An Obstetrics and Gynecology International Journal

Review

HJOG 2017, 16 (2), 1-12

Prediction of Gestational Diabetes Mellitus in the first trimester of pregnancy

Eleftheriades M[1], Karopoulou E[1], Papastefanou I[2], Kappou D[3], Sotiriadis A[4], Chrousos G[5].

[1]2nd Department of Obstetrics and Gynecology, National and Kapodistrian University of Athens Medical School, Aretaieio Hospital, 76 Vas. Sophias Ave, GR-11528, Athens, Greece
[2]Maternal - Fetal Medicine Unit, 4 Monis Petraki str,GR-11521, Athens, Greece
[3]1st Department of Obstetrics and Gynecology, National and Kapodistrian University of Athens Medical School, Alexandra Hospital, 80 Vas. Sophias Ave, GR-11528, Athens, Greece
[4]2nd Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, Thessaloniki, Greece
[5]1st Department of Pediatrics, National and Kapodistrian University of Athens Medical School, Aghia Sophia Children's Hospital, Thivon & Papadiamandopoulou str, GR-11527, Athens, Greece

Correspondence
Makarios Eleftheriades, Aretaieio Hospital, 76 Vas. Sophias Ave, GR-11528, Athens, Greece, E-mail: makarios@hotmail.co.uk

Abstract

Gestational diabetes mellitus (GDM) is defined as any degree of carbohydrate intolerance with onset or first recognition during pregnancy. This entity has been increasing in prevalence and has been associated with various maternal and perinatal adverse outcomes. There is much controversy about the diagnostic criteria and management of GDM and current screening models are based on maternal and obstetric characteristics, all lacking of strong positive predictive value. Placenta Growth Factor, Interleukin 6 and Osteocalcin are three biochemical markers that can be identified in maternal blood during the first trimester of pregnancy and there is evidence that their serum concentration is altered in pregnancies complicated by GDM. The aim of this review is to present the role of the abovementioned three biomarkers in the pathophysiology of GDM and their potential contribution in the development of a first trimester predictive model for GDM to detect women at risk early in pregnancy.

Key words: GDM, Fist trimester screening, PlGF, IL-6, OCN, Pregnancy, Glucose

Introduction

Gestational Diabetes Mellitus (GDM), one of the most common metabolic disorders of pregnancy, is defined as any degree of carbohydrate intolerance with onset or first recognition during pregnancy [1]. Normal pregnancy is characterized by pancreatic beta cell hyperplasia and increased insulin secretion. Furthermore, it is associated with "physiologic" maternal insulin resistance that develops in the second

trimester and peaks in the third trimester of pregnancy, as a result of increased placental secretion of diabetogenic hormones, such as Corticotropin-releasing Hormone (CRH), Human Placental Lactogen (HPL), Cortisol, Oestradiol and Oestriol and Progesterone. These alterations of maternal carbohydrate metabolism aim to assist glucose and amino acid transfer though the placenta for normal fetal growth and to provide the mother with free fatty acids, ketones, and glycerol as extra energy sources.

GDM develops when the pregnant woman is not able to produce an adequate insulin response to compensate for this physiologic insulin resistance[2,3]. Approximately 8-10% of pregnancies worldwide are complicated with GDM, which is associated with adverse outcomes, both maternal and fetal. These outcomes include not only short-term complications, such as preeclampsia, macrosomia, increased risk of operative delivery (caesarean or instrumental vaginal), shoulder dystocia and its associated complications: brachial plexus injury and fracture, neonatal hypoglycemia, hyperbilirubinemia, hypocalcemia, hypomagnesemia, polycythemia and respiratory distress syndrome, but also long-term conditions, such as maternal development of type II diabetes mellitus (T2DM), and increased offspring's risk of developing obesity, impaired glucose tolerance and T2DM, metabolic syndrome and cardiovascular disease.

Although studies have shown that early diagnosis and management of GDM can reduce the risk of adverse outcomes, there is still no consensus regarding either screening or the criteria that are used for diagnosis. One of the main controversies is whether the oral glucose tolerance test (OGTT) should be offered to all pregnaFnt women or to pregnant women with risk factors only [4,5].

National Institute of Health and Care Excellence (NICE) recommends risk assessment of GDM using risk factors in a healthy population. During the first prenatal visit, risk factors, such as BMI above 30 kg/m^2, previous macrosomic baby weighing 4.5 kg or above, previous GDM, family history of diabetes mellitus (first-degree relative with diabetes mellitus) or minority ethnic family origin with a high prevalence of diabetes mellitus are determined and women with any of these factors are identified as high risk for GDM. A 75g 2-hour OGTT is offered to all women with risk factors at 24-28 weeks, except for women with previous GDM. This group is offered either early self-monitoring of blood glucose or a 75g 2-hour OGTT as soon as possible after booking and a further 75g 2-hour OGTT at 24–28 weeks, if the results of the first OGTT are normal. Diagnosis is made when a fasting plasma glucose level is > 100 mg/dl or a 2-hour plasma glucose level is > 140 mg/dl [6].

American Diabetes Association (ADA) proposes two methods for the diagnosis of GDM: the "one step" procedure and the "two step" procedure. While universal screening is recommended by ADA, pregnant women are still screened selectively based on risk factors. Among other traditional risk factors for GDM, ADA's risk factors also include polycystic ovary syndrome, arterial hypertension and conditions related to insulin resistance. In the "one step" procedure a 75gr2-our OGTT is performed at women without history of diabetes at 24-28 weeks of gestation. In the "two step" procedure a 50gr OGTT is performed at women without preexisting diabetes regardless of last meal at 24-28 weeks and if plasma glucose (PG) at 1-hour after load is ≥ 140mg/dl then a 100g 3-hour OGTT after overnight fasting is performed. Diagnosis is made when two or more of PG are equal or higher: fasting PG of 95 mg/dl or 105 mg/dl, 1-hour PG of 180 mg/dl or 190 mg/dl, 2-hour PG of 155 mg/dl or 165mg/dl and 3-hour PG of 140 mg/dl or 145 mg/dl [7].

In 2011, the International Association of Diabetes and Pregnancy Study Group (IADPSG) proposed new guidelines for the diagnosis of GDM

based on the results of Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study. The study was conducted in 2008 and included 25,505 pregnant women who were tested with a 2-hour 75g OGTT and were followed throughout pregnancy. The results showed a linear association between maternal glucose and risk of adverse pregnancy outcomes. IADPSG criteria recommend screening high risk women at their first antenatal visit, visit for pre-existing diabetes and universal screening with a 75 g 2-hour OGTT after 8 hour overnight fasting at 24-28 weeks. GDM is diagnosed if any one of the following cut-off is met: fasting PG ≥ 92 mg/dl or 1-hour PG ≥ 180 mg/dl or 2-hour PG ≥ 153mg/dl. These criteria were endorsed by WHO and many other health associations worldwide and are the most commonly used guidelines for the diagnosis of GDM today ([8,9]) (Table 1).

outcome than the 100-gram three-hour oral GTT. The 75-gram OGTT increased sensitivity could be associated to the fact that only one elevated glucose value is required for a positive test and to its slightly lower cut-offs [10].

However, in 2013, a Eunice Kennedy Shriver National Institute of Child Health and Human Development Consensus Development Conference on diagnosing gestational diabetes recommended that the two-step approach for GDM diagnosis and screening should be preferred granted that there is no evidence that using the one-step approach and the 2-hour OGTT test thresholds would lead to clinically significant improvements in maternal or newborn outcomes, but would rather lead to a significant increase in health care costs. This recommendation is supported by The American College of Obstetricians and Gynecologists [1].

Table 1: Diagnostic criteria for GDM by various Groups/Organisations

	WHO/ RANZCOG*	ADA 1 step*	ADA 2 steps^	IADPSG*	EASD*	NDDG^	NICE*	ACOG^	Carpenter and Coustan
Glucose Challenge	2 hr 75 g OGTT	2 hr 75 g OGTT	1) 1 hr 50 g (non- fasting) screen, If 1 hr ≥140mg/dl proceed with step 2 2) 3 hr 100gr OGTT	2 hr 75g OGTT	2 hr 75 g OGTT	3 hr 100g OGTT	2 hr 75 g OGTT	3 hr 100gr OGTT	3 hr 100gr OGTT
Fasting	92mg/dl	92mg/dl	95 or 105mg/dl	92mg/dl	93.6mg/dl	105mg/dl		95.4mg/dl	95,4mg/dl
1 hour	180mg/dl	180mg/dl	180 or 190mg/dl	180mg/dl		190mg/dl		180mg/dl	180mg/dl
2 hour	153mg/dl	153mg/dl	155ή 166mg/dl	153mg/dl	162 mg/dl	165mg/dl	140mg/dl	155mg/dl	154.8mg/dl
3-hour			140 ή 145mg/dl			145mg/dl		140.5mg/dl	140mg/dl

* At least one of the following glucose value met or exceeded, ^ At least two of the following glucose value met or exceeded

ADA:American Diabetes Assocaton, EASD: European Association for the Study of Diabetes,WHO:World Healt Organization, RANZCOG:Royal Australian and New Zealand College of Obstetricians and Gynaecologists, IADPSG: International Association of Diabetes and Pregnancy Study Groups, NDDG:National Diabetes Data Group, NICE: National Institute of Health and Care Excellance, ACOG: American Congress of Obstetricians and Gynecologists

The 75-gram two-hour oral GTT seems to be more convenient, better tolerated, and more sensitive for identifying the pregnancy at risk for adverse

Recent studies have demonstrated the potential value of developing prognostic models to identify patients at risk for GDM in the first trimester of preg-

nancy. This could provide enough time for interventions to reduce both GDM rates and pregnancy and neonatal adversities associated with GDM. Many of these studies have examined the first trimester maternal serum levels of biochemical factors associated with insulin resistance, inflammation and oxidative stress in pregnancies subsequently complicated with GDM, but only a limited number of them suggest combining biochemical markers, measured early in pregnancy, with maternal and obstetric characteristics into a predictive model [11,12]. The use of inflammatory and other biomarkers to improve understanding of the pathophysiology of adverse pregnancy outcomes related to GDM has been proposed by current studies. Placenta Growth Factor (PlGF), Inteleukin-6 (IL-6) and Octeocalcin (OCN) are three biomarkers associated with the pathways that are involved in the pathophysiology of GDM [5,13,14].

The aim of this review is to present the potential roles of first trimester maternal serum levels of PlGF, IL-6 and OCN as predictive biomarkers of developing GDM and their contribution in early screening by developing prognostic models. This first trimester differentiation between high risk and low risk pregnancies could lead towards a more tailored care in pregnancy regarding GDM.

PlGF

The placenta plays an essential role in affecting pregnancy outcome and most pregnancy adversities are associated with defects of early placental development [15]. Therefore, assessment of maternal serum concentration of biomarkers, such as placental derived factors, has been suggested for investigation of perinatal outcomes.

Placental growth factor (PlGF) is a placenta-derived angiogenic protein implicated in angiogenesis, vasculogenesis and trophoblastic invasion of the maternal spiral arteries [16]. Maternal serum PlGF concentrations may differ depending on maternal and pregnancy characteristics, such as gestational age at sampling, weight, smoking status, method of conception, maternal racial origin and history of diabetes mellitus. Its role as a first trimester predictive parameter for pregnancy complications related to impaired placentation, such as preeclampsia (PE) and fetal growth restriction (FGR), has been widely studied. Furthermore, maternal serum PlGF concentration at 11-13 weeks of gestation is significantly lower in pregnancies complicated with trisomy 21, 18 and 13 [17].

There is a limited number of studies that have examined the potential role of first trimester maternal

Table 2. Maternal factors and pregnancy outcomes for the GDM group and the control group

Variable	Control group N=94	GDM N=40	p group value for univariate comparisons
Maternal age in years [a]	30(4.12)	33(4.2)	p=0.002 d
Maternal weight in Kg [a]	63 (8.9)	69(12.7)	p=0.009 d
Height in cm [a]	165(27.8)	165(31.5)	p=0.364 d
Parity [b]	15.95%	37.5%	p=0.005 e
Smoking status [b]	4.25%	15%	p=0.028 e
Gestational age at delivery in days [a]	275(8.2)	275(8.2)	p=0.476 d
Birth weight in gr [a]	3265(393)	3315(399)	p=0.375 d
Birth weight z-scores [c]	-0.1075789 (0.8986414)	-0.2100814 (0.9243586)	p =0.7249 f

Abbreviations: GDM, gestational diabetes mellitus. [a] Skewed variables, data presented as median (standard deviation) [b] Dichotomous variables presented as percentages. [c] Normally distributed variables, data presented as mean (standard deviation). [d] Non parametric Mann–Whitney U test. [e] Chi-square test for categorical variables. [f] Student's t-test, with Levene's test for equality of variances.

Adapted with permission

Table 3. Distributions of ultrasound, and biochemical parameters in the GDM and control groups

Variable	Control group N=94	GDM N=40	p group value for univariate comparisons
CRL in mm Median (SD)	60.3 (6.1)	61.2 (4.9)	Mann Whitney p = 0.213
NT in mm Median (SD)	1.6 (0.36)	1.8 (0.47)	Mann Whitney p = 0.216
FHR in b/min Mean (SD)	162.12 (6.58)	159.7 (5.87)	t - testp = 0.109
log_{10} MoM PAPP-A Mean (SD)	0.0208 (0.20)	-0.023 (0.19)	t - test p =0.300
log_{10} MoM free b hCG Mean (SD)	0.0035 (0.24)	0.0032(0.29)	t - test p =0.996
PlGF	58.94 (27.45)	48.17 (24.69)	t- test p < 0.001
Log $_{10}$ PlGF	1.76 (0.19)	1.68 (0.15)	p = 0.0085

Abbreviations: GDM, gestational diabetes mellitus; CRL, crown rump length; NT, nuchal translucency; FHR, fetal heart rate; log10 MoM PAPP-A, log10 transformed multiples of the median of pregnancy associated plasma protein-A; log10 MoM f b-hCG, log10 transformed multiples of the median of free b-human chorionic gonadotrophin; PlGF, placental growth factor; log10 PlGF, log10 transformed values of placental growth factor.

Adapted with permission

PlGF as a predictive factor for GDM. In 2014, Eleftheriades et al. conducted a case control study to examine maternal serum concentrations of PlGF at 11-14 weeks of gestation in pregnancies that developed GDM. The cohort consisted of 40 GMD cases and 94 controls. Maternal pregnancy characteristics, as well as biophysical and biochemical markers including PlGF, were taken into account (Tables 2, 3). The study showed that maternal PlGF was increased at 11-14 weeks in low risk pregnancies that developed GDM (Figure 1) and that the measurement of PlGF improved the performance of early screening for GDM provided by maternal factors alone, reaching a sensitivity of 71.4% for 25% FPR.

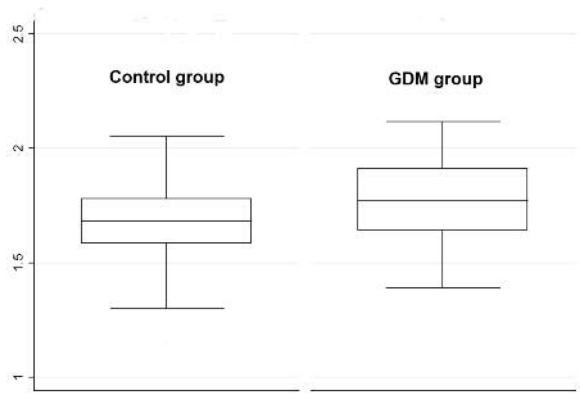

Figure 1. Maternal serum levels of log10 PLGF at 11 to 14 weeks in the control and the GDM groups. (Adapted with permission)

(Table 4) [5]. This prognostic model underwent external validation and showed acceptable discrimination and calibration [18].

Syngelaki et al. (2015) came to different conclusion during their attempt to investigate whether first trimester PlGF is altered in pregnant women that developed GDM and to evaluate its contribution to a first trimester screening model for GDM that combines maternal characteristics, medical history and biochemical markers. The study population consisted of 31.225 singleton pregnancies, 787 of which developed GMD. PlGF was measured in the serum of all pregnant women during their routine screening for pregnancy complications at 11-13 weeks and although it was found elevated in the GDM group, the performance of screening for GDM at 11-13 weeks was not improved by the addition of PlGF [19]. The authors reported as study limitation the method of identifying the GDM affected pregnancies, because the diagnostic OGTT was not carried out in all pregnancies studied, resulting in a possible overestimation of the performance of screening of their method.

Ong et al. (2004) also found that the level of maternal PIGF was increased in pregnancies with GDM, as well as in those with noninsulin dependent diabetes mellitus, but not in the insulin-dependent

Table 4. Detection rates for different false positive rates (FPR), for the various prediction models

Parameters for the Prediction Model	5% FPR	10% FPR	25% FPR
Maternal weight+maternal age	16.2%	32.4%	59.4%
PLGF	20%	37.1%	48.6%
Maternal weight+maternal age + PLGF	25.7%	34.29%	71.4%
$\log_{10}$ MoM IL 6	16.2%	18.9%	51.3%
Maternal weight+maternal age + $\log_{10}$ MoM IL6	28%	32.4%	64.9%
OCN	9.1 %	18.1 %	42.4 %
Maternal weight + Maternal age + OCN	22.2 %	33.3 %	72.2 %

Adapted with permission

diabetes group compared to controls [20].

Conversely, the study of *Mosimann et al*. (2016) reported that early measurement of maternal PlGF at 8-14 weeks was not altered in pregnant women who later developed GDM (21). The authors reported as exclusion criteria pre-existing diabetes type 1 or 2 and a first-trimester HbA1c value of ≥ 6.5%. However, no information was provided on pregnancy disorders associated with placental dysfunction, such as hypertensive disease, pregnancies resulting in intra-uterine death or pregnancies diagnosed with severe early onset growth restriction, as the above mentioned conditions have been associated with lower PlGF concentrations (22).

GDM induced hyperglycemia is associated with abnormal placental development and subsequent poor perinatal outcome and several studies have detected increased concentrations of angiogenic factors due to GDM-related hyperglycemia [15,23].

Furthermore, there is evidence that PlGF plays an important role in blood vessel formation at the maternal-fetal interface [24]. GDM studies found increased placental longitudinal vascular growth and enhanced branching angiogenesis and, therefore, alterations in PlGF expression in GDM may favor angiogenesis in placenta tissue and possibly explain the increase in the number of terminal microvilli and the increased degree of capillarization. Additionally, increased PlGF levels may also reveal a compensatory mechanism to maintain homeostasis in response to placenta hypoxia induced by hyperglycemia [25].

Further large prospective studies are necessary to clarify the impact of PlGF as a first trimester predictive biomarker of GDM.

IL-6

Obesity is increasing in prevalence worldwide and is involved in the development of pregnancy complications, such as PE and GDM [26]. In the United States, the National Center for Health Statistics data for 2011 to 2014 showed that 34.4 % of women aged 20 to 39 years were obese [body mass index (BMI ≥30 kg/m^2), with the prevalence being higher in non-Hispanic black women (56.9 %) [27].

Adipose tissue is considered as an active endocrine organ producing, when in excess, adverse effects on metabolic, vascular, and particularly inflammatory pathways in many organ systems, thereby affecting obstetric outcome. Among others, adipose tissue secretes several unique adipokines, as well as pro-inflammatory cytokines, such as Tumor Necrosis Factor (TNF)-α and IL-6, associated with the pathogenesis of insulin resistance during pregnancy in the case of obese women [28]. Elevated inflammatory response induced by adipocytokines locally (adipose tissue, placenta and vascular endothelium), as well as systemically, may be related to pregnancy complications. Considering that adiposity is associated with a systemic smoldering inflammatory

process during pregnancy and that there is a proportional relation between macrophages within the fat and the degree of adiposity, excess adipose tissue results in increased macrophage recruitment and further secretion of pro-inflammatory cytokines [26].

IL-6 is an inflammatory cytokine produced by immune and immune accessory cells, such as T cells and macrophages, provokes immune responses and acts on a wide variety of tissues and cells [26]. Prospective studies have shown that GDM is related to the up-regulation of IL-6. This increase in circulating IL-6 is present in women with GDM at delivery. Alterations in the expression of IL-6 assist glucose homeostasis in pregnancy by two ways: the direct way that involves insulin sensitivity and secretion and the indirect that involves inflammation, adipogenesis and, consequently, affected glucose metabolism. IL-6 also promotes the secretion of cortisol and growth hormone that contribute to insulin resistance and hyperglycemia. Increased IL-6 levels have been detected in both obese pregnancies and non-obese pregnancies complicated with GDM and, therefore, IL-6 might serve as a predictor of GDM [13,26,29,30].

Most published studies have investigated alterations in IL-6 levels in late second or third trimester of pregnancy at the time of screening for GDM. *Morisset et al*. (2011) reported that IL-6 levels were significantly higher in the serum of GDM patients than control pregnant women at the time of screening for GDM (26.1±3.7 weeks), as well as two months post-partum, irrespectively of obesity [31]. Moreover, *Kuźmicki et al*. (2014) measured IL-6 concentrations in the serum of pregnant women diagnosed with GDM at 24-28 weeks of gestation and in the serum of pregnant women with normal glucose tolerance who had similar BMI values with the GDM group also at 24-28 weeks. They found that GDM patients had higher serum IL-6 than women with normal glucose tolerance [28].

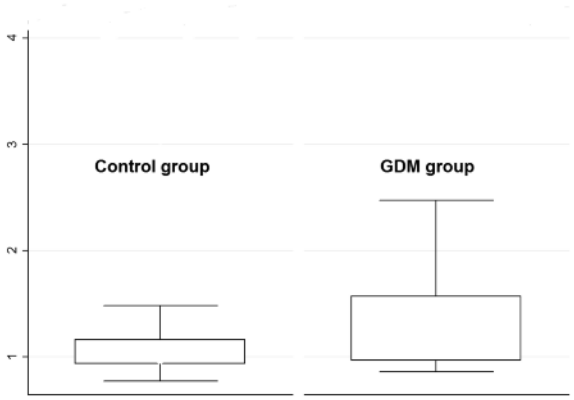

Figure 2. IL – 6 multiples of the median inthe GDM and the control group. (Adapted with permission)

The above mentioned findings were confirmed by *Nergiz et al*. (2014), who found significantly higher levels of IL-6 in pregnant women with GDM than those with normal glucose tolerance. The mean gestational age of the study participants was 31 + 4.7 weeks [32].

In 2014, *Hassiakos et al*. were the first to investigate circulating IL-6 concentrations in relation to GDM at 11-14 weeks of gestation. The authors showed that IL-6 concentrations were increased at 11–14 weeks in low risk pregnancies complicated with GDM (Figure 2) and that the combination of maternal characteristics and maternal serum IL-6 levels could provide effective first trimester screening for GDM, reaching a sensitivity of 64.9% for a false positive rate of 25% (Table 4) [13].

There is evidence that IL-6 concentrations correlate positively with percent body fat, BMI, insulin sensitivity and plasma glucose levels during pregnancy. The clarification of the impact that the imbalance in expression of pro-inflammatory and anti-inflammatory hormones has on impaired glucose homeostasis could contribute to the improvement of GDM screening [26]. Given that alterations in IL-6 in the serum of GDM patients were observed at 11-14 weeks and that inflammation is implicated in the pathogenesis of the disease long time before

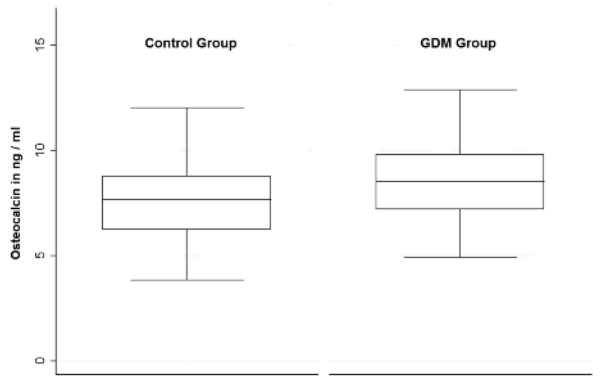

Figure 3. Osteocalcin in the gestational diabetes (GDM) and control groups.. (Adapted with permission)

its manifestation, IL-6 could serve as an effective marker for the development of first trimester screening model for GDM [13].

Osteocalcin

During pregnancy, there is a transfer of minerals across the placenta to the fetus, as the latter is totally dependent on maternal resources to ensure adequate mineral supply. There are two phases of bone reaction during pregnancy. The first phase, the early one, takes place at 12-14 weeks and is characterized by bone resorption, while the second phase, the later one, takes place at 38-40 weeks and is characterized by bone formation. Alterations in insulin resistance that normally occur during pregnancy and become more intense in GDM are responsible for hormonal changes that also affect bone loss. Furthermore, modifications in collagen glycosylation that occur because of hyperglycemia-related conditions, such as GDM and T2DM is considered as another mechanism proposed for lower bone competence. Therefore, pregnancies complicated with GDM are more often affected by alterations in bone turnover. Contrary to bone resorption markers that increase abruptly during the first trimester, concentrations of bone formation markers, except osteocalcin rise at the third trimester [33].

Osteocalcin is an osteoblast-derived protein with an established role as a bone formation and bone turnover marker. Recently, extra-skeletal roles of OCN in controlling glucose and energy metabolism in pancreatic β-cells, as well as in adipose and skeletal muscle tissue, have been reported and there have been many studies that evaluated the relations between osteocalcin and metabolic syndrome, cardiovascular disease and T2DM. Moreover, clinical studies have indicated that serum OCN levels are inversely associated with fasting glucose and insulin levels, as well as insulin resistance, suggesting that osteocalcin is important for glucose metabolism. There is a positive feedback mechanism between bone, pancreatic β-cells and adipose and muscle tissues, with insulin enhancing osteocalcin production, which in turn enhances insulin production through the proliferation of pancreatic β-cells, and tissue sensitivity to insulin. Most studies that investigated the association of T2DM and OCN showed decreased serum levels of OCN. [14, 34-38]. Studies investigating the association between OCN and GDM are limited and their results controversial.

In 2010, *Winhofer et al*. reported that serum OCN concentration was higher in pregnancies complicated with GDM than in women with normal glucose tolerance and supported a correlation between OCN and indices of insulin secretion in pregnancy [38]. These findings were consistent with results reported by Hossein-*Nezhad et al.* who showed that OCN levels were significantly higher in the GDM group than pregnant controls without GDM [33]. OCN concentration was measured in the third trimester of pregnancy in both studies. In contrast, there are also published studies demonstrating no significant differences in maternal serum OCN concentration between GDM patients and controls in the third trimester [39,40].

Only two studies have investigated alteration in maternal serum OCN at 11-14 weeks and its asso-

ciation with GDM. *Tabatabaei et al*. reported that OCN levels were significantly higher in the GDM group at 11-14 weeks than in the control group, but this difference had no predictive value for the development of GDM [41]. *Papastefanou et al*. (2015) studied the relation between OCN and GDM and evaluated the potential role of OCN as a first trimester predictive marker for the development of GDM in low risk pregnant women. They showed that maternal OCN concentration at 11-14 weeks was higher in pregnant women that developed GDM later in pregnancy (Figure 3) and in contrast to *Tabatabaei et al*., OCN combined with maternal and pregnancy characteristics could contribute to the development of a prediction model for GDM early in pregnancy. Thus, OCN combined with maternal age and maternal weight resulted in predicting 72.2% of GDM cases for a 25% FPR (Table 4). The authors suggested that increased OCN concentration could stimulate insulin secretion to allow meeting the increased insulin demands related to GDM and, therefore, this first trimester OCN alteration could promote an early mechanism of adaptation to the evolving insulin resistance, by inducing insulin secretion even before the clinical manifestation of the disease. Thus, the inclusion of OCN in a screening model for the prediction of the disease at 11-14 weeks could be beneficial for detection of women at risk in the first trimester of pregnancy and allow early interventions that could subsequently lead to decreased GDM prevalence [14].

Conclusions

Pregnant women are currently screened for GDM at 24 to 28 weeks of gestation and an increasing number is diagnosed with the disease, that parallels the obesity epidemic. GDM exposes both fetus and mother to potential short- and long-term complications. Although treatment of GDM can reduce the risk of adverse perinatal outcomes, preventive approaches of lifestyle modification, such as a healthy diet, to avoid excessive weight gain, and regular moderate exercise can reduce the risk of developing GDM. Moreover, GDM screening appears to be cost-effective in preventing development of type 2 diabetes mellitus, especially in populations with a high prevalence of GDM, as this disease is increasingly recognized as an opportunity for early prevention over the entire lifespan [42].

Thus, it seems that there is a clinical need for prediction of GDM early in pregnancy. PlGF, IL-6 and OCN are three biomarkers that relate to GDM and could serve as promising early predictive parameters for its development [5,13,14]. Maternal and pregnancy characteristics could be combined with PlGF, IL-6 and OCN concentrations during the first trimester into a novel prognostic model of the disease.

Women at risk for GDM identified in the first trimester of pregnancy could follow lifestyle modifications earlier than usual in pregnancy. Early interventions could improve maternal health, pregnancy outcome, long-term health of the offspring and reduce the incidence of GDM. Large-scale prospective studies involving diverse groups of subjects are warranted to clarify the association between first trimester PlGF, IL-6, OCN and other potential useful biomarkers with GDM.

References

1. Committee on Practice Bulletins—Obstetrics. Gestational diabetes mellitus. *Obstet Gynecol.* 2013;122(2 pt 1):406-416.
2. Farina, A., Eklund, E., Bernabini, D., et al. (2016). A First-Trimester Biomarker Panel for Predicting the Development of Gestational Diabetes. *Reproductive Sciences*, 1933719116675057.
3. Savvidou, M., Nelson, S. M., Makgoba, M., Messow, C. M., Sattar, N., & Nicolaides, K. (2010). First-trimester prediction of gestational diabetes mellitus: examining the potential of combining

maternal characteristics and laboratory measures. *Diabetes*, 59(12), 3017-3022.

4. Syngelaki, A., Visser, G. H., Krithinakis, K., Wright, A., & Nicolaides, K. H. (2016). First trimester screening for gestational diabetes mellitus by maternal factors and markers of inflammation. *Metabolism*, 65(3), 131-137.
5. Eleftheriades, M., Papastefanou, I., Lambrinoudaki, I. et al. (2014). Elevated placental growth factor concentrations at 11–14weeks of gestation to predict gestational diabetes mellitus. *Metabolism*, 63(11), 1419-1425.
6. https://www.nice.org.uk/
7. Rani, P. R., & BeGuM, J. (2016). Screening and Diagnosis of Gestational Diabetes Mellitus, Where Do We Stand. Journal of clinical and diagnostic research: *JCDR*, 10(4), QE01.
8. Mishra, S., Rao, C. R., & Shetty, A. (2016). Trends in the Diagnosis of Gestational Diabetes Mellitus. *Scientifica*, 2016.
9. International Association of Diabetes and Pregnancy Study Groups Consensus Panel. (2010). International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes care*, 33(3), 676-682.
10. Sacks, D. A., Hadden, D. R., Maresh, M. et al. (2012). Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel–recommended criteria. *Diabetes care*, 35(3), 526-528.
11. Kane, S. C., da Silva Costa, F., & Brennecke, S. (2014). First trimester biomarkers in the prediction of later pregnancy complications. Bio-*Med research international*, 2014.
12. Brink, H. S., van der Lely, A. J., & van der Linden, J. (2016). The potential role of biomarkers in predicting gestational diabetes. *Endocrine Connections*, 5(5), R26-R34.
13. Hassiakos, D., Eleftheriades, M., Papastefanou, I. et al. (2016). Increased maternal serum interleukin-6 concentrations at 11 to 14 weeks of gestation in low risk pregnancies complicated with gestational diabetes mellitus: Development of a prediction model. *Hormone and Metabolic Research*, 48(01), 35-41.
14. Papastefanou, I., Eleftheriades, M., Kappou, D. et al. (2015). Maternal serum osteocalcin at 11–14 weeks of gestation in gestational diabetes mellitus. *European journal of clinical investigation*, 45(10), 1025-1031.
15. Chang, S. C., & Vivian Yang, W. C. (2013). Hyperglycemia induces altered expressions of angiogenesis associated molecules in the trophoblast. *Evidence-Based Complementary and Alternative Medicine*, 2013.
16. Tsiakkas, A., Duvdevani, N., Wright, A., Wright, D., & Nicolaides, K. H. (2015). Serum placental growth factor in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound in Obstetrics & Gynecology,* 45(5), 591-598.
17. Wright, D., Syngelaki, A., Bradbury, I., Akolekar, R., & Nicolaides, K. H. (2014). First-trimester screening for trisomies 21, 18 and 13 by ultrasound and biochemical testing. *Fetal diagnosis and therapy*, 35(2), 118-126.
18. Lamain-de Ruiter, M., Kwee, A., Naaktgeboren, C. A. et al. (2016). External validation of prognostic models to predict risk of gestational diabetes mellitus in one Dutch cohort: prospective multicentre cohort study. *Bmj*, 354, i4338.
19. Syngelaki, A., Kotecha, R., Pastides, A., Wright, A., & Nicolaides, K. H. (2015). First-trimester biochemical markers of placentation in screening for gestational diabetes mellitus. *Metabolism*, 64(11), 1485-1489.
20. Ong, C. Y., Lao, T. T., Spencer, K., & Nicolaides, K. H. (2004). Maternal serum level of placental

growth factor in diabetic pregnancies. *Journal of reproductive medicine-Chicago-*, 49, 477-480.

21. Mosimann, B., Amylidi, S., Risch, L. et al. (2015). First-Trimester Placental Growth Factor in Screening for Gestational Diabetes. *Fetal diagnosis and therapy,* 39(4), 287-291.
22. Griffin, M., Seed, P. T., Duckworth, S. et al. (2017). Prediction of delivering a small for gestational age infant and adverse perinatal outcome in women with suspected pre-eclampsia. *Ultrasound in obstetrics & gynecology*
23. Leach, L. (2011). Placental vascular dysfunction in diabetic pregnancies: intimations of fetal cardiovascular disease?. *Microcirculation*, 18(4), 263-269.
24. Weel, I. C., Baergen, R. N., Romão-Veiga, M. et al. (2016). Association between placental lesions, cytokines and angiogenic factors in pregnant women with preeclampsia. *PLoS One*, 11(6), e0157584.
25. Pietro, L., Daher, S., Rudge, M. V. C. et al. (2010). Vascular endothelial growth factor (VEGF) and VEGF-receptor expression in placenta of hyperglycemic pregnant women. *Placenta*, 31(9), 770-780.
26. Abell, S. K., De Courten, B., Boyle, J. A., & Teede, H. J. (2015). Inflammatory and other biomarkers: role in pathophysiology and prediction of gestational diabetes mellitus. *International journal of molecular sciences*, 16(6), 13442-13473.
27. Ogden, C. L., Carroll, M. D., Fryar, C. D., & Flegal, K. M. (2015). Prevalence of obesity among adults and youth: United States, 2011–2014. *NCHS data brief*, 219(219), 1-8.
28. Kuźmicki, Mariusz, et al. "The IL-6/IL-6R/sgp130 system and Th17 associated cytokines in patients with gestational diabetes." *Endokrynologia Polska* 65.3 (2014): 169-175.
29. Pantham, P., Aye, I. L. H., & Powell, T. L. (2015). Inflammation in maternal obesity and gestational diabetes mellitus. *Placenta*, 36(7), 709-715.
30. Bao, W., Baecker, A., Song, Y., Kiely, M., Liu, S., & Zhang, C. (2015). Adipokine levels during the first or early second trimester of pregnancy and subsequent risk of gestational diabetes mellitus: a systematic review. *Metabolism*, 64(6), 756-764.
31. Morisset, A. S., Dubé, M. C., Cote, J. A., Robitaille, J., Weisnagel, S., & Tchernof, A. (2011). Circulating interleukin-6 concentrations during and after gestational diabetes mellitus. *Acta obstetricia et gynecologica Scandinavica*, 90(5), 524-530.)
32. Nergiz, S., Altınkaya, Ö. S., Küçük, M. et al. (2014). Circulating galanin and IL-6 concentrations in gestational diabetes mellitus. *Gynecological Endocrinology*, 30(3), 236-240.
33. Hossein-nezhad A., Hossein-nezhad A., Zh, M., Kh, M., Rahmani, M., & Larijani, B. "Osteocalcin and cross laps status among women with gestational diabetes mellitus during pregnancy." *Journal of Diabetes and Metabolic Disorders* 9 (2010): 7
34. Kanazawa, I. (2012). Diabetes mellitus and osteoporosis. The regulation of glucose metabolism by bone. *Clinical calcium*, 22(9), 1375-1382.
35. Kanazawa, I. (2015). Osteocalcin as a hormone regulating glucose metabolism. *World journal of diabetes*, 6(18), 1345-1354.
36. Zanatta, L. C., Boguszewski, C. L., Borba, V. Z., & Kulak, C. A. (2014). Osteocalcin, energy and glucose metabolism. *Arquivos Brasileiros de Endocrinologia & Metabologia*, 58(5), 444-451.
37. Ducy, P. (2011). The role of osteocalcin in the endocrine cross-talk between bone remodelling and energy metabolism. *Diabetologia*, 54(6), 1291.

38. Winhofer, Y., Handisurya, A., Tura, A. et al. (2010). Osteocalcin is related to enhanced insulin secretion in gestational diabetes mellitus. *Diabetes care*, 33(1), 139-143.
39. Saucedo, R., Rico, G., Vega, G. et al. (2015). Osteocalcin, under-carboxylated osteocalcin and osteopontin are not associated with gestational diabetes mellitus but are inversely associated with leptin in non-diabetic women. *Journal of endocrinological investigation*, 38(5), 519-526.
40. Telejko, B., Kalejta, K., Kuzmicki, M. et al. (2015). The association of bone turnover markers with pro-and anti-inflammatory adipokines in patients with gestational diabetes. *Annals of Agricultural and Environmental Medicine*, 22(2).
41. Tabatabaei, N., Giguère, Y., Forest, J. C., Rodd, C. J., Kremer, R., & Weiler, H. A. (2014). Osteocalcin is higher across pregnancy in Caucasian women with gestational diabetes mellitus. *Canadian journal of diabetes*, 38(5), 307-313.
42. Lohse, N., Marseille, E., & Kahn, J. G. (2011). Development of a model to assess the cost-effectiveness of gestational diabetes mellitus screening and lifestyle change for the prevention of type 2 diabetes mellitus. *International Journal of Gynecology & Obstetrics,* 115, S20-S25.

Received 15-4-2017
Revised 15-5-2017
Accepted 5-6-2017