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Gestational Diabetes and the Metabolic Syndrome

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1. Introduction

The metabolic syndrome is a clustering of traditional cardiometabolic risk factors that include central obesity, dysglycemia, hypertension, hypertriglyceridemia, and reduced high-density lipoprotein (HDL) cholesterol. In recent years, its clinical utility, diagnostic criteria and underlying etiology have been the subject of continuous debate and controversy. While the debate continues, it remains incontrovertible that those identified with the metabolic syndrome are at high risk for the future development of type 2 diabetes (T2DM) and cardiovascular disease (CVD). In addition, an expanding body of evidence has linked the metabolic syndrome with several emerging non-traditional risk factors, including markers of hepatic fat, chronic inflammation (such as C-reactive protein (CRP)), and adipocyte dysregulation (such as low circulating levels of adiponectin). Interestingly, many of these features of the metabolic syndrome are also common to gestational diabetes mellitus (GDM). Indeed, GDM has also been the subject of longstanding debate throughout its history and it too identifies women who are at high risk of developing T2DM and CVD in the future. Moreover, in recent years, GDM has been similarly linked to an array of non-traditional cardiometabolic risk factors, including CRP and hypoadiponectinemia. A series of studies have demonstrated that women with GDM are at risk of developing the metabolic syndrome in the years following their index pregnancy. Furthermore, emerging evidence shows that components of the metabolic syndrome identified in early gestation and even prior to pregnancy can predict the subsequent development of GDM. Taken together, these findings have raised the intriguing possibility that women who develop GDM may have an underlying latent metabolic syndrome that warrants clinical evaluation and risk factor modification.

Though intricate and still incompletely understood, the gradual expansion of knowledge about inter-relationships between the metabolic syndrome, GDM and T2DM may provide us with opportunities to screen for and detect metabolic dysfunction at various stages of disease progression. In this way, GDM represents an important and early “metabolic flag” for an affected mother and, perhaps, her offspring. Thus, in this chapter, we explore the emerging relationship between GDM and the metabolic syndrome. We review the definitions of each condition, their limitations and controversies, and their utility and predictive value in identifying T2DM and CVD risk. The clinical evidence for metabolic syndrome as a precursor to the development of GDM and, in turn, T2DM is also discussed.

Emerging non-traditional risk factors for both metabolic syndrome and GDM will be described, alongside the evidence for metabolic syndrome as a consequence of GDM and as a potential predictive tool to detect risk for GDM before and during early pregnancy. Finally, we consider the concept that women who develop GDM may have a latent metabolic syndrome.

2. Metabolic syndrome

2.1 General definition and varying sets of diagnostic criteria

The metabolic syndrome, also referred to as the insulin resistance syndrome, was initially proposed as a model for understanding the underlying biology and risk factors for CVD. In his Banting award lecture, Gerald Reaven first described 'Syndrome X' as the clustering of abnormalities related to insulin resistance (Reaven, 1988). The World Health Organization formally proposed the term 'metabolic syndrome' in 1998 (Alberti et al., 1998; DeFronzo & Ferrannini, 1991) to identify those at high risk for metabolic disorders and CVD. Though the syndrome was originally intended to identify individuals at risk for CVD, it has since expanded to capture those at high risk for T2DM, with which it is thought to have a stronger association (Ford et al., 2008). The definition of metabolic syndrome continues to evolve today, and is widely studied as a promising marker of cardiovascular risk.

The syndrome is characterized by a clustering of central abdominal (visceral) obesity, glucose intolerance, insulin resistance, dyslipidemia and hypertension (Reaven, 1988). The presence of any one risk factor implies the existence of others, such that their concomitant occurrence collectively describes a positive dysmetabolic risk profile for CVD, or 'cardiometabolic risk' (Despres et al., 2008).

While several organizations and authoritative bodies have proposed diagnostic criteria for the metabolic syndrome, the most cited working definitions are those of the International Diabetes Federation (IDF), the World Health Organization (WHO), and the National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATP III) (Alberti et al., 2005; WHO Expert Consultation, 2004; Alexander et al., 2003). These authorities have synthesized, analyzed and translated information gathered from a vast, globally representative body of research studies, in order to provide a set of diagnostic criteria with clinically relevant thresholds and measurements that can identify the metabolic syndrome and hence the risk of diabetes and CVD. Despite continued efforts, there are variations in the definitions, which have prompted international debate about the actual utility and strength of the metabolic syndrome as a diagnostic tool. Table 1 lists the criteria and diagnostic thresholds defined by the IDF, WHO, NCEP ATP-III, and, lastly, the recently published harmonized criteria (discussed in section 2.2).

Although the ATP III and IDF definitions differ in their diagnostic threshold criteria for metabolic syndrome, both include the same 5 components: increased adiposity, hypertriglyceridemia, low levels of high density lipoprotein cholesterol (HDL-C), hypertension and dysglycemia. The WHO definition also includes a urine albumin to creatinine ratio. Meeting the dichotomous cut-off points for an abnormality in 3 or more of the 5 components fulfills the requirements for diagnosis according to the ATP III definition (Hunt et al., 2004). Though all definitions include an obesity criterion, the IDF definition provides ethnicity-specific values for diagnosing abdominal obesity (Reaven, 2009). Moreover, for diagnosing metabolic syndrome, the IDF definition requires the presence of increased waist circumference (WC) as a necessary prerequisite along with any 2 of the

other criteria. Elevated triglycerides and/or low HDL-C must fall within the prescribed threshold or can be applied if a person is being treated specifically for the lipid abnormality. In addition, the defining criteria consider those with T2DM, an elevated WC and at least 1 other risk factor as having metabolic syndrome. The WHO requires the presence of diabetes, impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or insulin resistance and at least 2 other criteria. Among the 3 definitions, the IDF and ATP III are more commonly cited within the recent literature. The prevalence of metabolic syndrome in U.S. adults is estimated to be approximately 22% to 34% using the ATP III definition and 39% when the IDF criteria are applied (Ford, 2005).

	NCEP-ATP III	IDF	WHO	Harmonized IDF/AHA
Central obesity	WC >102 cm- (M) WC >88 cm- (F)	WC >94 cm- White (M) WC >80 cm- White (F) WC >90cm- Asian (M) WC >80cm- Asian (F)	Waist-to-hip ratio: >0.90- (M) >0.85- (F)	Same as IDF cut points for non-Europeans & either IDF or AHA criteria for Europeans
Elevated triglycerides	≥1.7 mmol/L	>1.7 mmol/L	≥1.7 mmol/L	≥1.7 mmol/L
Reduced HDL-C	<1.0 mmol/L- (M) <1.3 mmol/L- (F)	<1.03 mmol/L- (M) <1.29 mmol/L- (F)	<0.9 mmol/L- (M) <1.0 mmol/L- (F)	<1.0 mmol/L- (M) <1.3 mmol/L- (F)
Elevated blood pressure	≥130/85 mm Hg	>130/85 mm Hg	≥140/90 mm Hg	Systolic ≥130 and/or diastolic ≥85 mmHg
Fasting hyperglycemia	≥6.1 mmol/L	>5.6 mmol/L or diabetes or IGT	Diabetes, IFG, IGT	≥5.6 mmol/L
Urine albumin: creatinine ratio	-	-	≥ 3.4 mg/mmol	-

Table 1. Various diagnostic criteria for the metabolic syndrome

2.2 Controversy regarding the metabolic syndrome

The debate surrounding the metabolic syndrome stems from disagreement about its definition and diagnostic criteria, alongside questions related to its pathogenesis, origins, and applicability across populations. However, despite this ongoing debate, central obesity and insulin resistance have been widely postulated (Lann & LeRoith, 2007) as comprising the fundamental basis of the metabolic syndrome. Categorically, the syndrome is influenced by the complex genetic, hormonal and nutritional origins of its individual component risk factors. Discrepancies among the commonly used NCEP-ATP III, IDF and WHO definitions of the metabolic syndrome, have contributed substantially to this debate. For example, ATP III and WHO differ in their criteria for blood pressure, and neither definition provides specific guidance on how to implement these diagnostic thresholds (i.e., whether to use abnormal systolic vs. diastolic or both; whether to obtain measures in a particular body position; or whether to calculate an averaged measure). Recently, the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) and IDF attempted to resolve such discrepancies with new harmonized criteria. These criteria, shown in Table 1, include (i) clarification of the blood pressure measurement to specify elevated levels of systolic and/or diastolic pressure and (ii) elimination of abdominal obesity as a mandatory

prerequisite, such that the presence of any 3 of the 5 criteria is sufficient for diagnosis of metabolic syndrome (Alberti et al., 2010). The ATP III and IDF definitions differ in their criteria for increased fasting glucose and central obesity (using WC) (Alberti et al., 2006; NCEP 2001) and while obesity is measured by WC according to the ATP III and IDF definitions, waist-to-hip ratio is used in the WHO definition. Furthermore, urine albumin-creatinine ratio is a criterion in the WHO definition, but is not found in the ATP III and IDF definitions, while several risk factors associated with insulin resistance are not considered in any of the definitions, including physical inactivity, family history, sex and age (Kahn et al., 2005).

Further complicating the controversy is the practical observation that, despite its centrality to the metabolic syndrome, contrasting evidence suggests that many overweight or obese individuals may, by any guideline, have normal metabolic profiles (Wildman et al., 2008), and are not prone to future development of metabolic syndrome. Similarly, among those who display metabolic syndrome, not all are obese (Bruce & Hanson, 2010). Some lean individuals are insulin resistant and exhibit increased cardiometabolic risk. In a study of otherwise healthy obese individuals and insulin resistant lean individuals with a family history of T2DM, obesity was associated with higher insulin resistance and diastolic blood pressure, but conveyed no difference in other metabolic markers. In addition, within each BMI category, insulin resistance independently predicted metabolic syndrome, while WC did not. Only when age was combined with WC (but not BMI) did obesity independently predict metabolic syndrome, and, even so, WC was less predictive of insulin resistance at higher WC values (Utzschneider et al., 2010). The authors concluded that insulin sensitivity is a stronger predictor of metabolic syndrome than obesity, and is better than WC at identifying obese individuals with an otherwise healthy metabolic profile. They also recommended employing metabolic testing among lean individuals with a first-degree relative with T2DM (Utzschneider et al., 2010). Nevertheless, even when weight is considered, cut-points used to define obesity are not universally agreed upon and may vary by ethnicity (Despres et al., 2008).

The use of different definitions of the metabolic syndrome has clouded our ability to compare findings across research studies. In addition, there is the question of whether the diagnostic criteria are too restrictive, missing those at highest risk, or, conversely, are too broad, resulting in an overestimation of the prevalence of metabolic syndrome. Considering its inherently chronic and progressive nature, it is reasonable to infer that indicators of dysmetabolism, especially in younger adults, underestimate its consequences for predicting T2DM and CVD. Indeed, manifestation may even occur at different time-points in the disease trajectory, such that risk factor assessment necessitates systematic evaluation across a spectrum of sub-diagnostic and diagnostic ranges standardized for age.

Another criticism of the metabolic syndrome is whether its value extends beyond that of its individual components. The criticism highlights both the redundancy of the classification as a 'syndrome' and the inadvertent undermining of the importance of the individual components. The diagnosis of metabolic syndrome, by any definition, has been studied in relation to the predictive value of the individual criteria. The Framingham study (Wilson et al., 2005) demonstrated no substantial increase in risk associated with clusters of 3 of the 5 metabolic syndrome criteria compared with clusters of only 2 traits. In contrast, data from the Third National Health and Nutrition Examination Survey (Ninomiya et al., 2004) indicated that each of the 5 components of metabolic syndrome was an independent

predictor of CVD. These studies illustrate the controversy over whether a diagnosis of metabolic syndrome provides more useful information about CVD risk than any of its individual components (Reaven, 2009). Furthermore, by the current definitions, it is unclear whether any one risk factor is more predictive than the other, in the form of a weighted hierarchy.

To address these criticisms, the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) issued a joint statement about the clinical utility of the metabolic syndrome; they recommended that clinicians evaluate and treat discrete risk factors, without diagnosing the metabolic syndrome, *per se* (Kahn et al., 2005). Specifically, rather than solely relying on diagnosis of metabolic syndrome, identification of one or more of its component features should prompt investigation for the presence of the other features. For the latter, one may also consider specific emerging risk factors not included in the existing definition, as outlined below.

2.3 Metabolic syndrome and the identification of future risk of T2DM and CVD

The IDF recommends screening for metabolic syndrome features in those with T2DM (Alberti et al., 2006, Alberti et al., 2005). While current recommendations are subject to criticism and controversy, they nevertheless provide a practical basis upon which to adopt management strategies. Individuals with metabolic syndrome have a 5-fold higher risk of developing T2DM (Alberti et al., 2010). Similarly, in a study from the UK that examined the prognostic impact of metabolic syndrome in T2DM, the investigators modified the ATP III definition to include BMI instead of WC, and found that the metabolic syndrome further predicted CVD incidence five years after the diagnosis of T2DM (Guzder et al., 2006).

Showing that dysglycemia predicts metabolic syndrome necessarily identifies a predictive potential for T2DM as well. This is so given that metabolic syndrome -- and especially glucose intolerance -- is central to the development of T2DM. In the GENFIEV study, metabolic syndrome prevalence was 42% in those with IFG, 34% in IGT, and 74% in IFG + IGT (Bianchi et al., 2010). In addition, the prevalence of insulin resistance was higher in those with metabolic syndrome than in its absence. Hypertriglyceridemia (odds ratio [OR] 3.38; 95% confidence interval [CI] 2.29-4.99), abdominal obesity (3.26; 95% CI 2.18-4.89), hyperglycemia (3.02; 95% CI 1.80-5.07) and hypertension (1.69; 95% CI 1.12-2.55) were all associated with insulin resistance. These findings suggest that the prevalence of the metabolic syndrome is high in individuals with dysglycemia, and is generally associated with insulin resistance (Bianchi et al., 2010). Moreover, dysglycemia and insulin resistance are highly predictive of T2DM. Similarly, long-term glycemic excursions will identify those at high risk for metabolic syndrome and T2DM. In their exploratory study, Giuffrida et al. (2010) investigated the relation between glycated hemoglobin (GHb), an indicator of long-term glycemic control, and metabolic syndrome with T2DM. Each 1% increase in GHb was associated with metabolic syndrome (OR 1.31, 95% CI 1.18-1.45), demonstrating a strong relation between chronic hyperglycemia and metabolic syndrome (Giuffrida et al., 2010).

Aboriginal Canadians have a 5-fold higher risk of T2DM compared to non-Aboriginals. Among the former, the metabolic syndrome can be readily identified using available clinical measures, and thus, may be a useful clinical tool (Reaven, 2009; Ley et al., 2009). In a prospective study, Ley and colleagues (2009) found that the 10-year cumulative incidence of T2DM in the Aboriginal Canadian population was 17.5%, with an age-dependent gradient ranging from 10.5% among those aged 10-19 years, to 43.3% among those aged 40-49 years.

The authors reported that, at baseline, metabolic syndrome had a low positive predictive value for future diabetes; however, the syndrome predicted incident diabetes to the same degree as IGT, while its high negative predictive value identified disease-free individuals at follow-up (Ley et al., 2009).

In addition to identifying those at risk of T2DM, metabolic syndrome also independently predicts risk of CVD. In the joint statement from the ADA and the EASD (2005), the authors emphasized the practical use of the metabolic syndrome, focusing on its predictive value for CVD (Kahn et al., 2005). A meta-analysis of a series of European trials reported that metabolic syndrome raises the hazard ratio for CVD in women from 0.6 to 2.8 (Hu et al., 2004). Moreover, patients with metabolic syndrome are at twice the risk of developing CVD over a 5-10 year period than those without the syndrome (Alberti et al., 2010). Several population studies have described an increased cardiovascular risk in the presence of metabolic syndrome (Alexander et al., 2003; Ford, 2004, 2005; Hunt et al., 2004; Isomaa et al., 2001; McNeill et al., 2005). Alexander and colleagues (2003) used the ATP III criteria to assess the prevalence of coronary heart disease (CHD) among patients with the metabolic syndrome. They reported that those without metabolic syndrome, regardless of diabetes status, had a low CHD prevalence (less than 10%), while those with diabetes but not the metabolic syndrome exhibited no increased risk of CHD (Alexander et al., 2003). Otherwise, metabolic syndrome was a significant predictor of CHD (OR 2.07, 95% CI 1.66-2.59) and conferred a risk beyond that of diabetes alone (Alexander et al., 2003).

In the San Antonio Heart Study, metabolic syndrome at baseline was a significant predictor of cardiovascular mortality over a mean follow-up of 13 years (Hunt et al., 2004). Similarly, using the WHO definition, Isomaa and colleagues (2001) found that the risk for CHD and stroke was increased 3-fold in those with the metabolic syndrome ($P < 0.001$), as was cardiovascular mortality ($P < 0.001$) (Isomaa et al., 2001). In a study of individuals without diabetes or CVD at baseline, the ATP III- defined metabolic syndrome had an adjusted hazard ratio of CHD of 1.46 (95% CI, 1.23-1.74) for men and 2.05 (95% CI, 1.59-2.64) for women (McNeill et al., 2005).

Ford and colleagues (2004) showed a linear association between ATP III-based metabolic syndrome and CVD-related mortality as well as all-cause mortality (Ford et al., 2004). A meta-analysis of worldwide data from studies published between 1998 and 2005, showed pooled relative risks (RR) of 1.27 (95% CI, 0.90-1.78) for all-cause mortality, 1.65 (95% CI, 1.38-1.99) for CVD and 2.99 (95% CI, 1.96-4.57) for T2DM using ATP III-defined metabolic syndrome; in the fewer studies that used the most exact WHO definition, the pooled RRs were 1.37 (95% CI, 1.09-1.74) for all-cause mortality and 1.93 (95% CI, 1.39-2.67) for CVD (Ford, 2005). Thus, there is considerable evidence for the predictive value of the metabolic syndrome for identifying risk of T2DM and CVD.

2.4 Metabolic syndrome and emerging non-traditional risk factors

As the components of metabolic syndrome continue to be better understood, the syndrome appears to be a promising diagnostic and screening tool. Recent studies have identified chronic low-grade inflammation as a systemic consequence of obesity that is related to both metabolic and vascular disease. For example, the inflammatory nature of atherosclerosis prompted the study of inflammatory proteins, such as high-sensitivity C-reactive protein (CRP), as potential predictors of CVD. Indeed, epidemiological studies have shown the independent relation between CRP and CHD (Ridker, 1997, 1998).

Nakano et al, (2010) investigated the clinical significance of LDL and CRP in coronary artery disease (CAD) risk (Nakano et al., 2010). Among those without the metabolic syndrome, high CRP was not associated with a higher risk of CAD; however, those with both high CRP and metabolic syndrome had a doubling in their risk of CAD (Ridker et al., 2003; Sattar et al., 2003). Despite uncertainty regarding the utility of adding CRP to the metabolic syndrome definition, investigation of its potential as a predictive tool and meaningful addition to metabolic syndrome is advocated (Ridker et al., 2004).

Previous studies have also examined the use of adipose tissue biomarkers, including adiponectin, in predicting CVD risk. Adiponectin is an adipocyte-derived polypeptide -- an adipokine -- that is inversely associated with obesity, insulin resistance and T2DM. As a protective adipokine, it inhibits gluconeogenesis and suppresses lipogenesis. Low levels of adiponectin result in reduced fatty acid oxidation and increased fat accumulation in the liver. Adipose tissue plays a central role to metabolic syndrome, and low adiponectin levels are associated with metabolic syndrome. In addition, the strong association between hypoadiponectinemia and CVD risk implicates adiponectin in the disease trajectory. Compared with lean controls, patients with metabolic syndrome and T2DM have lower circulating levels of total and high molecular weight (HMW) adiponectin, and higher levels of leptin and interleukin-6 (IL-6). Decreased total and HMW adiponectin, and increased levels of leptin and IL-6, are characteristic of patients with metabolic syndrome and T2DM (Lee et al., 2009). There may also be a link between low adiponectin and fatty liver disease (Matsubara et al., 2004).

Hepatic dysregulation is characterized by insulin resistance -related steatosis and oxidative stress (Kim & Younossi, 2008). Non-alcoholic fatty liver disease (NAFLD) -- ranging from simple steatosis (fatty infiltration) to inflammatory steatohepatitis (NASH), to long-term injury (fibrosis) -- is a strong indicator of insulin resistance in non-pregnant adults (Youssef & McCullough, 2002). The process of NAFLD development is in itself an extension of insulin resistance that reduces free fatty esterification and triglyceride storage in adipose tissue, subsequently resulting in the deposition of free fatty acids in non-adipose tissues, especially the liver (Utzschneider & Kahn, 2006). Hence, NAFLD is considered to be the principal liver manifestation of the metabolic syndrome (Kim & Younossi, 2008), as it requires the presence of insulin resistance and is closely associated with T2DM (Targher et al., 2005). In a recent study of adults with newly diagnosed T2DM, there was significant interplay between T2DM and liver injury, likely explained by NAFLD (Porepa et al., 2010). NAFLD may also be detected with the novel serum marker, Fetuin-A, an endogenous inhibitor of insulin receptor tyrosine-kinase, and a recognized "hepatokine". Elevated plasma Fetuin-A levels positively predict the incidence of T2DM independent of other established risk factors (Ix et al., 2008; Stefan et al., 2008). In a study of 330 adults at risk for T2DM, liver fat was the strongest predictor of prediabetes (Kantartzis et al., 2010) (Kantartzis et al., 2010). Among studied biochemical measures, serum Fetuin-A was a more significant predictor of fasting hyperglycemia than serum adiponectin (Kantartzis et al., 2010). In addition, individual liver enzymes, such as alanine aminotransferase, have varying positive associations with the components of the metabolic syndrome (Zhang et al., 2010).

While hyperuricemia is prevalent among those with metabolic syndrome, its clinical utility remains controversial. Nonetheless, it appears to be a predictor of metabolic syndrome. One hypothesis is that enhanced insulin resistance due to fatty acid synthesis in the liver may be linked to additional purine synthesis, thereby accelerating production of uric acid. Since insulin resistance is considered an underlying mechanism connecting visceral obesity and

metabolic syndrome (Matsuura et al., 1998), it follows that insulin resistance is related to elevated serum uric acid levels in those with metabolic syndrome (Borges et al., 2010). While a sex-dependent association between hyperuricemia and metabolic syndrome is apparent, there is no current evidence for its association with sex hormones. Sex hormone binding globulin (SHBG) is a liver-derived glycoprotein regulated by insulin, which inhibits its production in hepatocytes. Low serum SHBG levels are associated with increased insulin resistance and hyperinsulinemia. In a recent review Brand et al. (2011) examined 52 observational studies and found that, for both sexes, metabolic syndrome was associated with low levels of SHBG (Brand et al., 2011).

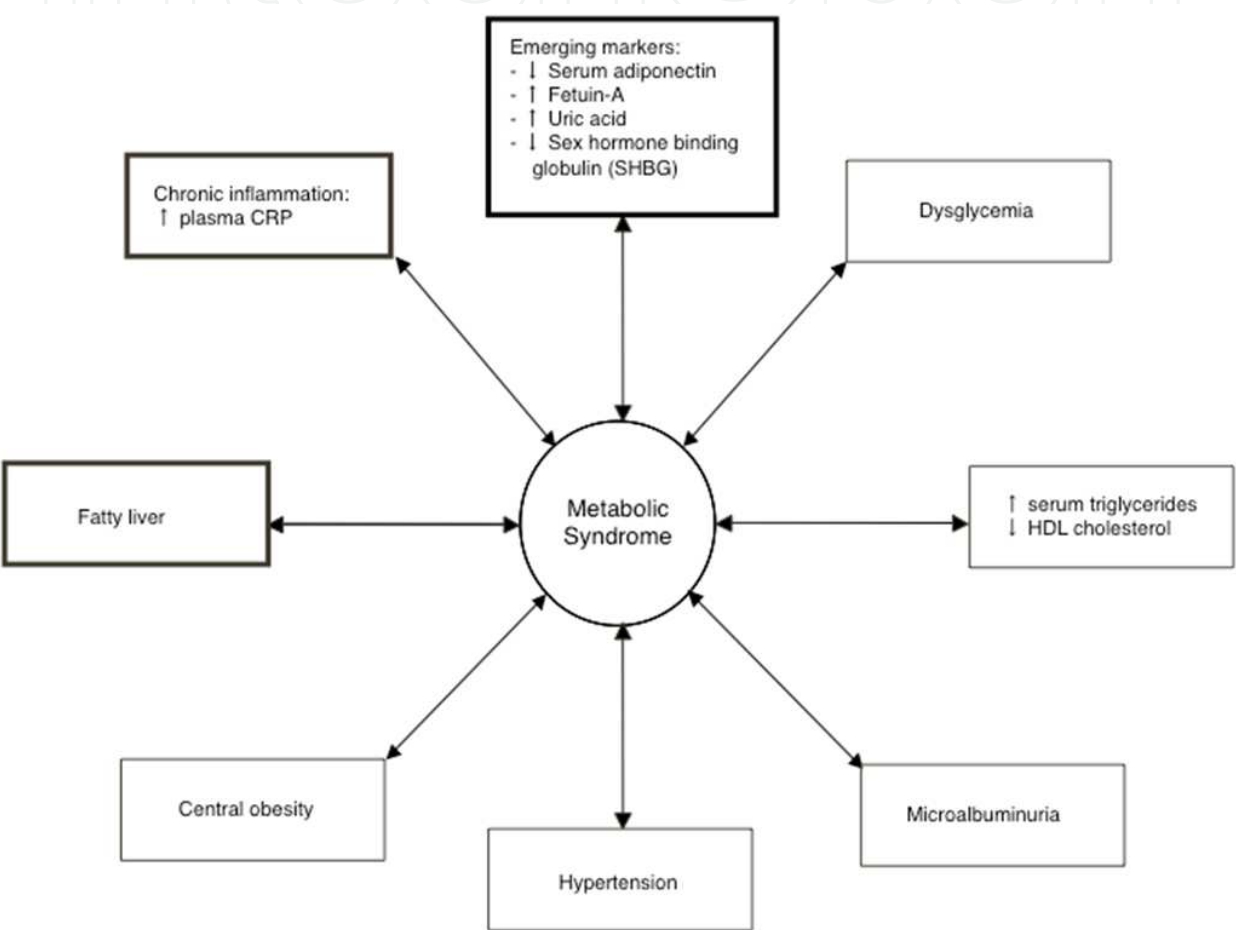


Fig. 1. Traditional & non-traditional (bolded) cardiometabolic risk factors associated with metabolic syndrome.

3. Gestational Diabetes Mellitus (GDM)

3.1 General definition and varying sets of diagnostic criteria

GDM, defined as glucose intolerance of varying severity with first onset in late pregnancy, bears many of the same risk factors as T2DM, including: older maternal age, a family history of T2DM, non-White ethnicity, obesity, sedentary lifestyle, and previous GDM (Dornhorst et al., 1992; Hedderson & Ferrera, 2008; Hillier et al., 2008; Ray et al., 2001). GDM has both short and long-term risks for a mother and her child. Acute maternal effects include pregnancy-induced hypertension and increased risk of Caesarian-section, while long-term

consequences include increased risks of T2DM and CVD. Neonatal complications include fetal macrosomia and the associated risk of shoulder dystocia (Athukorala et al., 2007) which in turn can lead to neonatal musculoskeletal and brachial plexus injury (Christoffersson & Rydhstroem, 2002), while long-term sequelae are childhood obesity (Metzger, 2007), metabolic syndrome, and higher risk of T2DM and hypertension (Athukorala et al., 2007; Boney et al., 2005; Joffe et al., 1998; Leon, 1998; Metzger, 2007; Reece et al., 2009). Though practices vary, many countries recommend that all pregnant women be screened at 24 to 28 weeks' gestation with a 1- hour 50-g glucose challenge test (GCT), followed by a confirmatory 2-hour 75-g, or 3-hour 100-g oral glucose tolerance test (OGTT). While a strategy of selectively screening only women at high risk of GDM may improve the true positive detection rates, some women without classical risk factors for GDM will be missed, accordingly. Table 2 outlines some commonly used diagnostic criteria for GDM.

	NDDG (National Diabetes Data Group)	ADA 2003	WHO 1999	IADPSG 2010 (Harmonized)
Diagnostic OGTT	3-h, 100-g	3-h, 100-g	2-h, 75-g	2-h, 75-g
OGTT-Fasting	5.8 mmol/L	5.3 mmol/L	7.0 mmol/L	5.1 mmol/L
OGTT-1 h	10.5 mmol/L	10.0 mmol/L	-	10.0 mmol/L
OGTT-2 h	9.2 mmol/L	8.6 mmol/L	7.8 mmol/L	8.5 mmol/L
OGTT-3 h	8.0 mmol/L	7.8 mmol/L	-	-
Abnormal values needed for diagnosis	≥2	≥2	≥1	≥1

Table 2. Diagnostic criteria for GDM according to commonly used definitions.

Despite variations in diagnostic criteria, the utility of these definitions for predicting clinical outcomes has been demonstrated. As an example, while the ADA and WHO diagnostic criteria for GDM differ slightly (International Association of Diabetes and Pregnancy Study Group [IADPSG], 2010), the antepartum 2-hour 75g OGTT predicts adverse pregnancy outcomes based on both criteria: the ADA criteria resulted in an increased risk of macrosomia (RR 1.29, 95% CI 0.73-2.18), preeclampsia (RR 2.28, 95% CI 1.22-4.16) and perinatal death (RR 3.10, 95% CI 1.42-6.47) (Schmidt et al., 2001) and similar results were observed using the WHO criteria. Some speculate that the restrictive diagnostic criteria for GDM may overlook the risks faced by women with lesser degrees of dysglycemia (Ferrara et al., 2007; Vambergue et al., 2000). Others assert that lack of international uniformity and agreement of diagnostic thresholds for GDM limits their utility within clinical settings (Metzger & Coustan, 1998). For example, the UK guidelines recommend that only high-risk groups be screened (IADPSG, 2010). In Canada, screening for GDM is routinely done, but not in a universal manner (Wen et al., 2000). Furthermore, current guidelines do not account for the variable risk attributed to ethnicity, in which there are considerable differences in the prevalence of GDM. In a study of ethnicity and postpartum metabolism in women with prior GDM, South Asian Indian women had higher serum triglycerides and lower HDL-C

levels, while African-Caribbean women had a higher WC, blood pressure, and insulin levels (Savitz et al., 2008).

3.2 Controversy regarding GDM

Like the metabolic syndrome, GDM has also been the subject of controversy, especially surrounding the timing of screening, the choice of diagnostic test, and the defining thresholds on these tests for its identification. Existing guidelines used to identify GDM, and hence the high risk of T2DM following pregnancy, were initially adapted from criteria that were applied to the non-pregnant population; they were not designed to identify those at risk for adverse perinatal outcomes (IADPSG, 2010). Extensive research has led to modifications of the definition (Cutchie et al., 2006) following the original publication of the criteria (O'Sullivan & Mahan, 1964). Of note, these original criteria were based on the identification of those women at risk of developing diabetes in the years after the index pregnancy (O'Sullivan & Mahan, 1964).

The clinical justification for screening for GDM currently focuses on the prevention of fetal macrosomia and associated obstetrical complications (Retnakaran et al., 2009c). Notably, this focus has resulted in a single set of diagnostic criteria used to identify women at risk for two different adverse outcomes (Retnakaran et al., 2009c), which effectively leads to the assumption that a diagnosis of GDM optimally identifies the risks of both macrosomia and postpartum prediabetes/diabetes. In a study designed to test this assumption, subjects representing the full spectrum of antepartum glucose tolerance underwent a 3-hour OGTT, and the results showed that only fasting glucose emerged as a significant predictor for delivery of a large-for-gestational-age (LGA) infant, with an OR of 2.0 (95% CI 1.20-3.34) per 1 mmol/L incremental increase (Retnakaran et al., 2009c). However, all three post-load measures were significant predictors of postpartum prediabetes/diabetes (1-h glucose: OR 1.37, 95% CI 1.17-1.61; 2-h glucose: OR 1.55, 95% CI 1.32-1.83; 3-h glucose: OR 1.30, 95% CI 1.10-1.53). Thus, fasting glucose values may better predict LGA risk, but post-load values better predict postpartum glucose intolerance (Retnakaran et al., 2009c). Clearly, an additional challenge to the GDM diagnostic definition includes how the results are applied.

The prevailing consensus within the existing framework for diagnosing GDM is that hyperglycemia, including levels below those for overt diabetes, is associated with the adverse pregnancy outcomes common to GDM. In addition, most agree that screening for GDM at 24-28 weeks' gestation identifies individuals in whom effective management can reduce glycemic excursions and minimize adverse perinatal outcomes. It remains to be determined, however, whether these current strategies can effectively reduce long-term risks of metabolic syndrome, T2DM and CVD in affected women (Nolan, 2011). Indeed, women who do not meet the prescribed thresholds for GDM may incur glucose-mediated fetal macrosomia (Mello et al., 1997; Rudge et al., 2000; Scholl et al., 2001; Sermer, et al., 1995), and may be at risk for T2DM and CVD (Retnakaran et al., 2008a, 2008b, 2009a, 2009b, 2009c, 2009d, 2009e, 2010c; Shah et al., 2008).

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study was undertaken to examine the risks associated with glucose values below traditional thresholds used to diagnose GDM. The study findings were translated by the IADPSG, in order to harmonize the existing diagnostic criteria (Table 2). The practical implications of these revised criteria includes the universal adoption of a 2-hour, 75-g OGTT. In doing so, these recommendations may identify an increased number of women at lower risk for

complications. How the IADPSG recommendations will impact the risk of long-term development of metabolic disease remains unknown at this time (IADPSG, 2010).

3.3 GDM and the Identification of future risk of T2DM and CVD

It is estimated that 20 to 60% of women with a history of GDM will eventually develop T2DM. Indeed, the relation between GDM and T2DM is well described, and the two conditions share a similar pathophysiology, characterized by insulin resistance of peripheral tissues and insufficient secretion of insulin by the pancreatic beta cells to compensate for this resistance (Buchanan, 2001; Buchanan & Xiang, 2005; Retnakaran et al., 2010a). Pregnancy itself has been described as a “stress test” for T2DM and CVD (Reece et al., 2009). It necessarily involves a state of severe acquired insulin resistance that is comparable to that of a non-pregnant person with T2DM (Bergman, 1989). Furthermore, adult offspring with prediabetes, born to women with previous GDM, display an 8-times higher risk of T2DM (Clausen et al., 2008), demonstrating the cyclical nature of diabetes (Damm, 2009) and the compounding effects of dysmetabolism in pregnancy.

Since O’Sullivan’s early research illustrating high rates of IGT in the years following GDM (O’Sullivan, 1991), many studies have investigated the phenomena of elevated risk of T2DM attributed to previous GDM. In their systematic review and meta-analysis to quantify the risk of T2DM following GDM, Bellamy and colleagues (2009) found that women with GDM had an increased risk of developing T2DM compared to those women who had normoglycemic pregnancies (RR 7.43, 95% CI 4.79-11.51 (Bellamy et al., 2009). Epidemiological evidence shows that, for all populations and ethnic groups, GDM increases the risk of T2DM (Ben-Haroush et al., 2004). While the shared risk factors between GDM and T2DM imply a common etiology, the salient message is that women with a history of GDM represent a highly vulnerable group for the development of T2DM. This is readily evident in the 2% prevalence of T2DM following GDM as early as 6 weeks postpartum, with reported rates of 50-60% at 5-10 years postpartum, and 70% by 28 years postpartum (Kim et al, 2002; Lauenborg et al., 2004). Furthermore, at the population level, the health significance of GDM is apparent in the number of individuals with diabetes preceded by GDM. In their meta-analysis of follow-up studies of women with previous GDM, Cheung and Byth (2003) calculated the population-attributable risk percent (PAR%) for the proportion of cases of T2DM associated with prior GDM. The PAR% ranged from 10-31% (Cheung & Byth, 2003). These data suggest that up to one third of parous women with T2DM have a history of GDM.

In addition to identifying women at risk for T2DM, GDM also has implications for future risk of CVD. Indeed, women with a history of GDM are at risk for sub-clinical atherosclerosis (Tarim et al., 2006). Studies also show an increased prevalence of cardiovascular risk factors in women with previous GDM (Carr et al., 2006; Lauenborg et al., 2005; Verma et al., 2002). Shah and colleagues (2008) used large population-based administrative databases to examine the CVD risk in women with a history of GDM. They found that, by 11.5 years after delivery, the hazard ratio for CVD in women with GDM was 1.71 (95% CI 1.08-2.69)(Shah et al., 2008). Moreover, even mild glucose intolerance in pregnancy is associated with an increased risk of CVD. Compared with normoglycemic women who did not receive an OGTT, those who had an abnormal GCT followed by an OGTT that was not diagnostic of GDM still had an increased risk of CVD within 12 years of the index pregnancy (Retnakaran & Shah, 2009b).

GDM likely increases the risk for developing cardiometabolic dysfunction after an affected pregnancy. In a longitudinal study comprising 12-18 years of follow-up, 45% of women with

previous GDM went on to develop hypertension compared to only 4% in the control group (Mestman, 1972). Another study demonstrated significantly higher rates of dyslipidemia, hypertension and mortality 26 years after GDM (O'Sullivan, 1991). Further exacerbating the burden of disease is family history of T2DM, which adds to the elevated risk associated with GDM. Carr and colleagues (2006) quantified the increased risk of CVD in women with GDM and a family history of T2DM, compared to women without a history of GDM (OR 1.85, 95% CI: 1.21-2.82) (Carr et al., 2006). It is generally recommended that women with GDM undergo a postpartum OGTT to detect ongoing dysglycemia. If lower thresholds for GDM are adopted, then more women are likely to be screened for T2DM postpartum. One hopes that this will offer a preventive opportunity that would otherwise be missed in these women.

3.4 GDM and emerging non-traditional risk factors

CVD is described as an inflammatory disease, with analogous findings in diabetes and obesity (Stern, 1995). Studies have also demonstrated the presence of inflammation in GDM, with high concentrations of serum CRP associated with GDM, but which are attenuated by further adjustment for BMI (Winzer et al., 2004; Wolf et al., 2003). In a cross-sectional study examining the role of maternal obesity in the association between CRP and GDM, pre-pregnancy BMI emerged as the most important determinant of serum CRP concentration, independent of GDM (Retnakaran et al., 2003). It thus emerges that obesity may mediate a systemic inflammatory response that underlies the relation between CRP and GDM.

Similar to its potential as a metabolic syndrome risk factor, adiponectin is also a promising marker of GDM. Compared to unaffected women, those with GDM have lower levels in pregnancy of both total and HMW adiponectin (Retnakaran et al., 2004; Retnakaran et al., 2007). These lower levels of total and HMW adiponectin are associated with both insulin resistance and pancreatic beta-cell dysfunction (Retnakaran et al., 2005; Retnakaran et al., 2007). Furthermore, hypoadiponectinemia in pregnancy independently predicts postpartum metabolic dysfunction, including fasting glycemia, insulin resistance and beta-cell dysfunction (Retnakaran et al., 2010d). Thus, hypoadiponectinemia may play a role in the development of T2DM in women with a history of GDM.

Another novel marker potentially associated with GDM is the presence of a fatty liver. In non-pregnant women with previous GDM who underwent MRI of the liver, those with high liver fat had elevated fasting serum triglyceride and insulin concentrations and lower whole-body insulin sensitivity than those with low liver fat on MRI (Tiikkainen et al., 2002). Given that NAFLD is common in T2DM, Forbes and colleagues (2011) investigated the prevalence and risk for NAFLD among European women with previous GDM. The prevalence of NAFLD was much higher in women with previous GDM (38%, 95% CI 28-47) than in those without GDM (17%, 95% CI 10-24) (Forbes et al., 2011).

Limited evidence exists for the association between uric acid and GDM, although its predictive value in T2DM makes it a promising candidate for studies of GDM. High uric acid levels have been detected in women with GDM (Seghieri et al., 2003), and are considered a marker of preeclampsia (Barden et al., 2004).

SHBG (Smirnakis et al., 2007) is another biochemical marker of much interest. Bartha et al. (2000) compared serum SHBG levels between women with and without GDM, and found that SHBG levels were lower in the GDM group (Bartha et al., 2000). Similarly, SHBG, in addition to adiponectin, was shown to be lower in women with GDM than unaffected controls (Nanda et al., 2011). Even when measured in early pregnancy, first-trimester SHBG

levels were lower among women who went on to develop GDM compared to their peers (187 nmol/L vs 233 nmol/L) (Thadhani et al., 2003).

In addition to traditional measures for GDM, these emerging risk factors are the same as those described for metabolic syndrome arising outside of pregnancy (Figure 2). Accordingly, they raise the question of whether the metabolic syndrome relates to GDM.

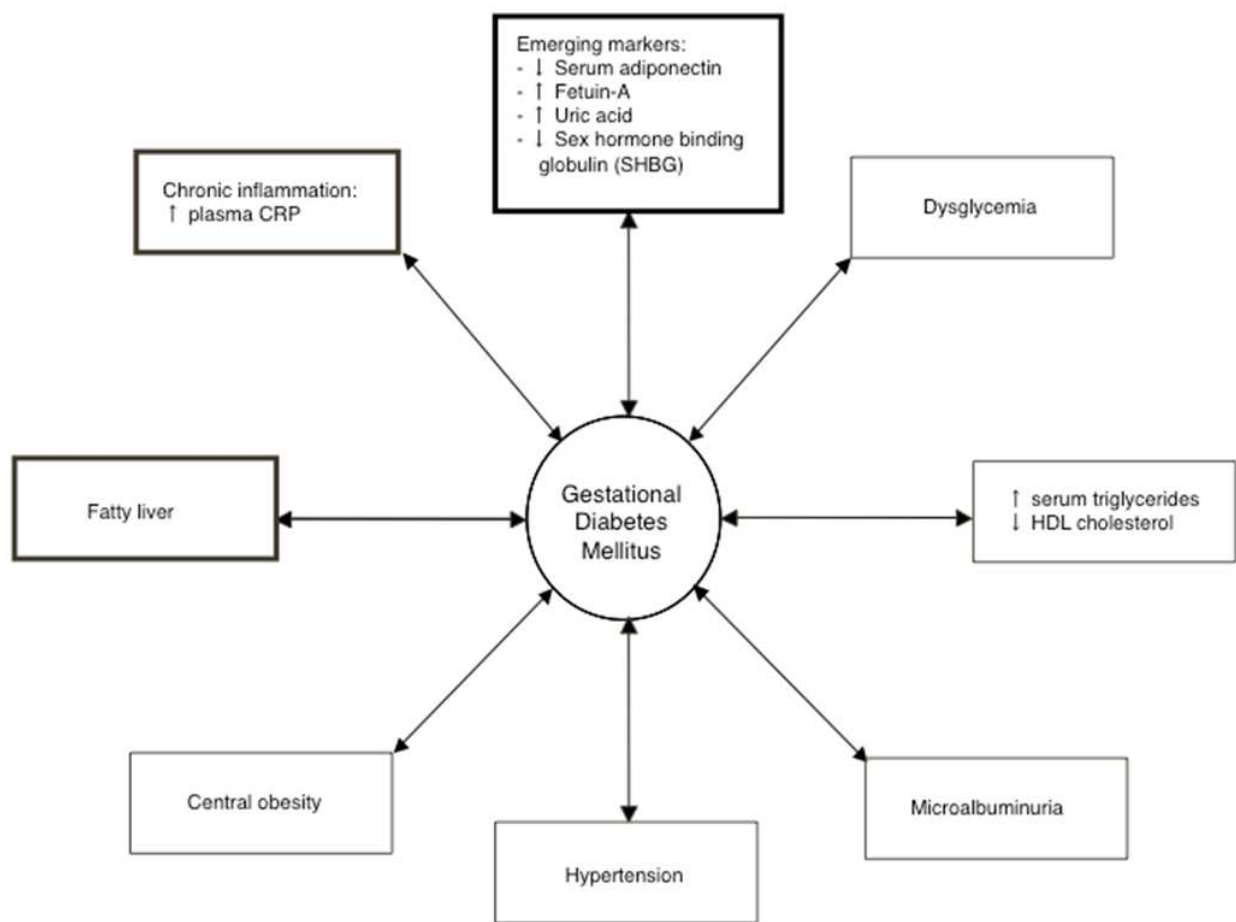


Fig. 2. Traditional and non-traditional (bolded boxes) cardiometabolic risk factors associated with GDM.

4. Risk of metabolic syndrome and its sequelae following GDM

4.1 Development of metabolic syndrome after GDM

Evidence that the metabolic syndrome both precedes and follows GDM suggests an increased lifetime risk of T2DM in women with prior GDM. In addition to chronic beta-cell dysfunction, women with GDM have chronic insulin resistance that is apparent after delivery. Indeed, in the decade after pregnancy, many women with previous GDM exhibit features of the metabolic syndrome. Considering the shared risk factors of metabolic syndrome and T2DM, and the similarities between GDM and T2DM, it is not surprising that GDM is likewise associated with metabolic syndrome. Akinci and colleagues (2010) collected antepartum characteristics of women who developed metabolic syndrome in their later years. Using the ATP III and IDF definitions for metabolic syndrome, pre-pregnancy obesity, weight gain, and OGTT fasting glucose levels each predicted the development of

metabolic syndrome. Moreover, even a fasting glucose concentration above 5.5 mmol/L at the antepartum OGTT was an independent predictor of metabolic syndrome (Akinci et al., 2010). Indeed, many studies have demonstrated an increased prevalence of features of the metabolic syndrome following GDM.

Egeland and Meltzer (2010) investigated the effects of GDM on future risk of metabolic and cardiovascular abnormalities. The prevalence of glucose intolerance at 15 years follow-up was 44.4% among women with prior GDM, vs. only 13.1% in those without GDM. WC at 15-year follow-up was the strongest predictor of this difference (Egeland & Meltzer, 2010). Similarly, in a U.S. study, the prevalence of the metabolic syndrome was 27.2% 11 years after pregnancy in women with previous GDM, compared to only 8.2% in unaffected controls (Verma et al., 2002). Lauenborg et al. (2005) estimated the risk of metabolic syndrome in a Danish cohort of women 9.8 years after delivery. Women with previous GDM had a 3-fold higher risk of metabolic syndrome compared to non-GDM controls (Lauenborg et al., 2005). A similar study in Europe reported prevalences of metabolic syndrome of 21% and 4.6%, respectively, 8.5 years' postpartum (Bo et al., 2004b). Indeed, prior gestational hyperglycemia in the absence of fulfilling the overt criteria for GDM results in a future risk of metabolic syndrome 2-4 times that of those with normoglycemia in pregnancy. This risk is 10 times higher in women with concomitant pre-pregnancy obesity (Bo et al., 2004a). Thus, even mild gestational hyperglycemia predicts metabolic syndrome (Bo et al., 2004b), and metabolic syndrome is increasingly more likely to develop over time following the index pregnancy (Bo et al., 2006). These studies highlight the chronic nature of the metabolic dysfunction associated with GDM. Furthermore, they raise the possibility that a diagnosis of GDM may indicate the presence of an underlying latent metabolic syndrome (Retnakaran et al., 2010b).

4.2 Development of metabolic syndrome in the early postpartum after GDM

Recent evidence implicates GDM as an early expression of metabolic syndrome (Haffner & Taegtmeier, 2003). Indeed, it was recently reported that both GDM (OR 2.05, 95% CI 1.07-3.94) and the milder state of gestational impaired glucose tolerance (GIGT) (OR 2.16, 95% CI 1.05-4.42) independently predict postpartum metabolic syndrome by 3 months postpartum, even after adjustment for covariates (Retnakaran et al., 2010d). Furthermore, by 3 months postpartum women with GDM and GIGT also exhibit non-traditional risk factors associated with metabolic syndrome, including low levels of adiponectin and increased serum CRP (Retnakaran et al., 2010c). While many of the metabolic disturbances of pregnancy resolve after delivery, growing evidence supports the concept that pregnancy provides an opportunity to observe a pronounced expression of an otherwise subclinical metabolic disorder. Such metabolic disturbances, which include the metabolic syndrome component disorders, may indeed be apparent prior to the diagnosis of GDM.

5. Prediction of GDM by metabolic syndrome components and associated risk factors

5.1 Prediction of GDM by metabolic syndrome components in early pregnancy

It is quite likely that the metabolic syndrome exists prior to the development of GDM. Indeed, GDM has even been proposed to be a component of the metabolic syndrome (Clark et al. 1997). In their study, Clark et al. (1997) showed that, at the time of their antepartum OGTT, women with GDM expressed markers of the metabolic syndrome, including low

serum HDL cholesterol and higher fasting plasma insulin, triglycerides, free fatty acids and pre-pregnancy BMI. These common features of the metabolic syndrome were each individually predictive of GDM, and persisted after adjustment for differences in BMI (Clark et al., 1997).

In addition to conventional measures of metabolic syndrome, several non-traditional biomarkers have also emerged as possible predictors of GDM. As discussed earlier, low adiponectin is a risk factor for T2DM and an emerging risk factor for metabolic syndrome and GDM. Using a prospective nested case-control study design, Williams et al. (2004) determined whether first trimester hypoadiponectinemia predicts GDM. They found that 73% of those with GDM had a low adiponectin level compared to 33% of controls (adjusted OR 4.6, 95% CI 1.8-11.6) (Williams et al., 2004). Similarly, Lain and colleagues (2008) found that women with low adiponectin concentrations in the first trimester were much more likely to be diagnosed with GDM (OR 10.2, 95% CI 1.3, 78.7) (Lain et al., 2008).

In choosing an optimal early serum marker to predict GDM, Smirnakis and colleagues (2007) compared SHBG, high-sensitive CRP, and the homeostasis model of assessment of insulin resistance (HOMA-IR) in late first trimester and early second trimester of pregnancy (Smirnakis et al., 2007). Serum SHBG was lower, and serum CRP higher, in women who went on to develop GDM, who also had elevated HOMA-IR in the second trimester. After multivariate analysis, SHBG emerged as the best predictor of GDM (Smirnakis et al., 2007). Alternately, Wolf et al. (2003) found that the risk of developing GDM was higher in women in the upper vs. lower tertiles of first-trimester CRP, after adjusting for confounders (OR 3.6, 95% CI 1.2-11.4). Importantly, the association was attenuated when BMI was included in the analysis (OR 1.5, 95% CI 0.4-5.5) (Wolf et al., 2003), suggesting that obesity confounds the relation between inflammation and GDM.

Qiu and colleagues (2004) found that, even after adjusting for maternal pre-pregnancy BMI and other confounders, women with CRP in the highest vs. lowest tertiles experienced a 3.5-times increased risk of GDM (95% CI 1.2-9.8) (Qiu et al., 2004). Moreover, even lean women had an OR for GDM of 3.7 (95% CI 1.6-8.7), suggesting that the association between elevated CRP and GDM may not solely depend on the presence of maternal obesity (Qiu et al., 2004). However, Savvidou and colleagues (2010) evaluated various first-trimester conventional and novel biomarkers, including adiponectin and CRP, and found only a low HDL-C and a high tissue plasminogen activator were significant independent predictors of GDM (Savvidou et al., 2010). Laughon et al (2009) reported that a first trimester concentration of uric acid in the highest quartile had an OR for GDM of 3.25 (95% CI 1.35-7.83), after adjusting for BMI and age (Laughon et al., 2009). Together, these emerging risk factors present an opportunity for early detection of GDM, and possibly, the identification of an effective tool for long-term prevention of metabolic syndrome.

It is likely that components of metabolic syndrome exist before and after GDM. Similar to T2DM, where persons with IGT and IFG are at significant risk of T2DM, so too may be the case for metabolic syndrome in early pregnancy. Ray and colleagues (2010) coined the term “gestational prediabetes” to describe the absence of diabetes before pregnancy, and the presence of a blood glucose level (or a related marker) in early pregnancy that is higher than normal, but not yet high enough to meet the diagnostic criteria for GDM (Ray et al., 2010). Given the promising findings of using emerging biomarkers to detect dysmetabolism in early pregnancy and predict GDM, the next step is to identify a robust biomarker that can be assayed at a low cost in early pregnancy. Since they are chronic in nature, metabolic

abnormalities likely precede pregnancy, which means that they should be detectable in early pregnancy as well.

5.2 Prediction of GDM by metabolic syndrome components prior to pregnancy

A modest body of literature exists about the existence of metabolic syndrome prior to the detection of GDM. Gunderson and colleagues (2009) examined pre-pregnancy cardiometabolic risk factors and the risk of GDM in subsequent pregnancies. They found that metabolic impairment often predated the onset of GDM, and that 27% of overweight women with one or more cardiometabolic risk factors developed GDM (Gunderson et al., 2009). Normoglycemia with at least one metabolic risk factor (i.e., low plasma HDL-C and/or hyperinsulinemia) was present before pregnancy in 34% of those who developed GDM; among overweight women, the presence of any cardiometabolic feature was associated with an almost 4 times higher risk of GDM. Hedderson and Ferrara (2008) measured blood pressure before pregnancy and in early pregnancy, and found that women with mild hypertension in early pregnancy had a small increased risk of GDM (OR 1.56, 95% CI 1.16-2.10). Those with frank hypertension had a 2-fold increased risk of GDM (OR 2.04, 95% CI 1.14-3.65) compared to normotensive women, even after adjusting for confounders. These findings were paralleled by mild (OR 1.44, 95 CI 0.95-2.19) and frank (OR 2.01, 95% CI 1.01-3.99) hypertension detected before pregnancy (Hedderson & Ferrara, 2008).

6. Conclusions

We have reviewed the parallels and associations between the metabolic syndrome and GDM. Both conditions have had multiple sets of diagnostic criteria and a history marked by controversies about their definition, clinical utility and significance. Both conditions identify a patient population that has an increased future risk of T2DM and CVD. Furthermore, both conditions have been associated with a similar set of emerging non-traditional risk factors. Consistent with these parallels, GDM predicts an increased risk of metabolic syndrome both in the early postpartum and in the years thereafter. Moreover, it is now becoming apparent that the metabolic syndrome and its associated risk factors may precede the diagnosis of GDM, both in early gestation and prior to the pregnancy. Taken together, these data suggest that GDM may represent a transient 'unmasking' of a latent metabolic syndrome, which may extend in both directions through (i) the pre-gravid state and early pregnancy, and (ii) the early and late postpartum. Figure 3 illustrates this lifetime continuum that may link metabolic syndrome, GDM, T2DM, and CVD. The chronic nature of the features of metabolic syndrome suggests that what we know about the temporal relation between metabolic syndrome, GDM, T2DM, and CVD is limited. The global burden of diabetes has been estimated at more than 171 million individuals with an expected increase to 366 million by 2030 (Wild et al., 2004). The prevalence of obesity and related metabolic dysfunction worldwide is a vivid demonstration of the indiscriminating potential of cardio-metabolic diseases across ethnicities and age groups. In this context, the emerging relation between metabolic syndrome and GDM may offer the opportunity for early detection of at-risk individuals, long before the manifestation of overt disease. Ideally, this opportunity may lead to new strategies for early risk modification and ultimately disease prevention. As such, the emerging relation between metabolic syndrome and GDM represents an important area of research that may hold both clinical and public health implications.

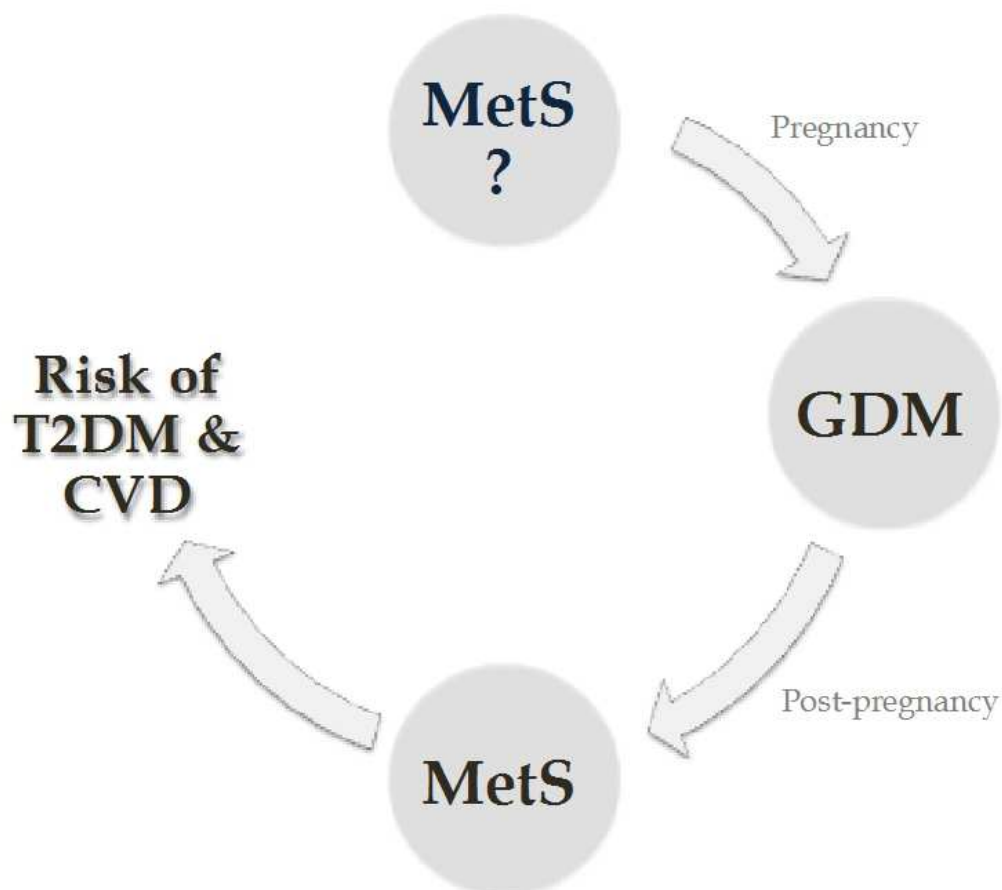


Fig. 3. Theoretical framework and conceptual model for latent metabolic syndrome preceding GDM.

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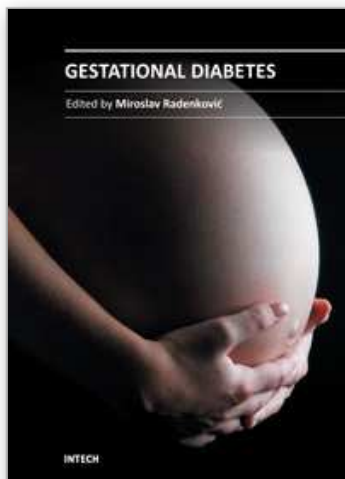
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Gestational diabetes mellitus is defined as hyperglycemia with onset or first recognition during pregnancy. The incidence of gestational diabetes is still increasing and this pathological condition has strong association with adverse pregnancy outcomes. Since gestational diabetes can have long-term pathological consequences for both mother and the child, it is important that it is promptly recognized and adequately managed. Treatment of gestational diabetes is aimed to maintain euglycemia and it should involve regular glucose monitoring, dietary modifications, life style changes, appropriate physical activity, and when necessary, pharmacotherapy. Adequate glycemic control throughout the pregnancy can notably reduce the occurrence of specific adverse perinatal and maternal outcomes. In a long-term prospect, in order to prevent development of diabetes later in life, as well to avoid associated complications, an adequate education on lifestyle modifications should start in pregnancy and continue postpartum.

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