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Ethnic Differences in the Risk of Developing Metabolic Syndrome or its Components in Women with a History of Gestational Diabetes Mellitus

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Abstract

Women with a history of gestational diabetes mellitus (GDM) are known to be at increased risk for diabetes and cardiovascular disease. Other cardiovascular risk factors that integrate the metabolic syndrome also seem to be more prevalent in this group of women. On the other hand, several studies have shown that there is an ethnic effect on disease risk. Prevalence of type 2 diabetes, gestational diabetes and other cardiovascular risk factors vary greatly in populations of different ethnicity. Therefore, we have reviewed the available evidence on the prevalence of the metabolic syndrome components in women with previous GDM along with the differential characteristics of each ethnic group.

Keywords: Gestational diabetes mellitus; Cardiovascular risk factors; Metabolic syndrome; Ethnicity; Type 2 diabetes mellitus

Introduction

Women with a history of GDM mellitus (GDM) are known to be at increased cardiovascular risk. These women require more non-invasive cardiac diagnostic procedures and present with more cardiovascular episodes and hospital admissions for cardiovascular reasons, compared to healthy controls [1]. One-third to one-half of women with a history of GDM will develop type 2 diabetes mellitus (T2DM) within 3-5 years [2,3], and this condition is a known risk factor for the development of cardiovascular disease. Moreover, metabolic and cardiovascular alterations that increases the risk of T2DM and cardiovascular disease cluster together in the metabolic syndrome, which is characterized by central body adiposity, dyslipidaemia, hypertension and elevated fasting glucose levels [4]. Because T2DM and metabolic syndrome share common risk factors, it is not surprising that previous GDM is associated with features of metabolic syndrome.

On the other hand, ethnicity is an indicator of many potential influences on health, including socio-economic position, discrimination, lifestyle factors such as diet and physical activity, medical care access and genetic heritage based on geographic origin. A number of important epidemiological discoveries regarding the origins of cardiovascular disease have been generated by seeking the causes of ethnic variation in disease risk [5,6]. The increased risk of T2DM in certain ethnic groups [7,8] as well as the known ethnic variation in the prevalence of obesity [9] encourages a closer look at ethnic variation in GDM and its consequences.

Given that women with a history of GDM have an elevated vascular risk, and that ethnic factors exert a strong effect, we considered it opportune to review the prevalence of the components of the metabolic syndrome in women with previous GDM, along with the available evidence about the differential characteristics of each ethnic group regarding metabolic syndrome components and cardiovascular risk.

Definition of ethnic groups

The current definition of ethnicity is arbitrary and ill defined, with significant variations in the terms used to define specific race/ethnic groups in the literature. Definition of ethnicity usually involves aspects such as cultural, economic, social and biological factors and geographical origins. In this respect, some ethnic groups have a marked heterogeneity, with different phenotypes, geography, culture and religion, and treating these subgroups as one racial group could mask the effects of ethnicity in health outcomes. This is particularly the case of the Asian population, which is often aggregated into a single ethnic group despite very different origins, such as Native Hawaiian, East Asian (Japan, China, Korea), South Asian (India, Pakistan, Bangladesh), Southeast Asian (Cambodia, Vietnam, Laos, Thailand) and Pacific Islanders (e.g., The Philippines). Therefore, to avoid masking outcome differences when the data are aggregated in studies evaluating ethnic differences, ethnic subgroups should be precisely defined.

On the other hand, there has been broad discussion of the use of biological race as a concept in human genome research. Some authors argue that race is not a scientific category and is not sufficiently precise or relevant to understanding human genetic diversity, while others hold that genetic information can be studied according to racial differences and is the best approach to studying genetic diversity [10].

Thus, trying to interpret the meaning of differences related to ethnicity is always a challenge. Despite the major limitations of using ethnicity as a predictive and explanatory variable in health research, there is still a dire need to conduct research on ethnic differences in health outcomes.

GDM and risk of type 2 diabetes

Many studies have assessed the risk of progression to T2DM after GDM [11-20] (Table 1). A major issue with all studies in this area, however, is their marked heterogeneity. The number of diagnostic criteria in clinical use for GDM diagnosis over the last four decades leads to the identification of cohorts that may not be directly comparable in terms of the severity of glucose intolerance. In women with a history of GDM, both the criteria and method used to diagnose diabetes and/or abnormal glucose tolerance have varied significantly. Furthermore, the ethnic mix of the cohorts studied is extremely heterogeneous, with some composed entirely of a single ethnicity and others showing very mixed composition. Finally, the length of follow-up varies between studies, from 6 weeks to almost 30 years. Despite these differences and the resulting difficulty of comparing incidence or prevalence of T2DM across studies, regardless of the criteria used it is clear that GDM signifies a high risk of future progression to T2DM.

	Study Type	Women studied	Mean follow-up	Predictive factors for developing type2 diabetes	Incidence of T2DM	Ethnicity
Bellamy et al. [2]	Review and meta-analysis, 2009	64 - 6,300	6 weeks to 28 years	Previous GDM, maternal age, waist circumference, use of insulin, previous obesity	5% - 37%	Mixed
Kim et al. [3]	Review, 2002	8 - 1,118	6 weeks to 28 years	Elevated fasting glucose levels	2.6% - 70%	Mixed
Carson et al. [11]	Review, 2013	700 GDM; 789 controls	12 weeks		1% - 25%	Mixed
Pallardo et al. [12]	Prospective cohort, 1999	788 GDM	4 months	Prepregnancy obesity, number of abnormal values in the 100 g OGTT.	5.4%	
Albareda et al. [13]	Prospective Cohort, 2003	696 GDM; 70 controls	11 years	Gestational age at the time of diagnosis of GDM<20 weeks, BMI previous to pregnancy<26.4	13.8%	White
Kjos et al. [20]	Prospective cohort and review, 1995	671 GDM	4 weeks to 6 years	Fasting glucose and gestational age at the time of GDM diagnosis	50%	Latin
Sinha et al. [15]	Retrospective cohort, 2003	221 GDM/IGT	6 to 12 weeks	In Afro-Caribbean family history of diabetes. In Indo-Asians insulin requerirment during pregnancy and diagnosis of diabetes prior to 20 week of pregnancy	Persistent glucose intolerance: 7% in White, 5% in Afro-Caribbean and 35% in Indo-Asians	White, Indo-Asian and Afro-Caribbean
Lee et al. [17]	Retrospective cohort, 2007	5.470 GDM; 783 controls	6 weeks to 15 years	Asian ethnicity and use of insulin in pregnancy	1% - 26%	White and Asian
Girgis et al. [18]	Prospective cohort and review, 2012	73 GDM; 28 controls	5.5 years	Use of insulin, hypertension in pregnancy	69% in South Asian 42% in South European and 39% in Australian born	White and Asian
Xiang et al. [19]	Retrospective cohort, 2011	13,000 GDM; 65,000 controls	4.5 years		9% in White, 12.7% in Hispanic, 16.5% in Black and 10.4% in Asian	White, Latin, Black and Asian

Table 1: Gestational diabetes and the incidence of type 2 diabetes mellitus

A meta-analysis by Bellamy et al. found that women with a history of GDM had 7.5 times higher risk of developing T2DM than those with normal carbohydrate metabolism in pregnancy [2]. Carson et al. reported a T2DM incidence in the first 6 months postpartum of women with GDM ranging from 1% to 25%, and of carbohydrate intolerance and elevated basal glycaemia of 5% to 32% and 2.5% to 32%, respectively [11].

Various studies in Spain have contributed data on abnormal postpartum glucose tolerance in Caucasian women. The first of these showed a diabetes incidence of 5.4%, increased basal glycaemia of 5.8% and carbohydrate intolerance of 10.4% at 4 months postpartum [12]. A later study by Albareda et al. described higher incidence rates after 11 years of follow-up: 13.8% for T2DM and 43% for increased basal glycaemia plus carbohydrate intolerance [13].

On the other hand, several studies have shown that ethnic groups with a high prevalence of T2DM have greater risk of GDM and of postpartum prediabetes [14]. In a retrospective study in the United Kingdom that included Indo-Asian, Caucasian and African-Caribbean women with a diagnosis of GDM that were evaluated between the sixth and twelfth weeks postpartum, the authors found that 35% of Indo-Asians presented with altered glucose metabolism (diabetes mellitus or impaired glucose tolerance) compared with 7% of Caucasians and 5% of African-Caribbeans [15]. In the Indo-Asian group, the predisposing factors for postpartum dysglycaemia were insulin requirement during pregnancy and a diagnosis of GDM before week 20 of the pregnancy. This would reflect higher rates of undiagnosed preGDM in Indo-Asian women. Among Caucasians and African-Caribbeans, no predisposing factors for postpartum glucose intolerance were found. Those of Indo-

Asian and African-Caribbean descent had higher incidence of family history of diabetes, compared with Caucasians, reflecting the increased prevalence of T2DM in these ethnic groups [16].

Lee et al. compared women of Caucasian and Asian descent (without specifying subgroups) in a retrospective cohort study in Australia with up to 15 years of follow-up in 6,989 patients with GDM and 780 controls [17]. They reported and accumulated T2DM incidence in GDM patients of 1.7% at one year postpartum and of 17% and 25% at 10 and 15 years, respectively. In this cohort, independent predictors of postpartum dysglycaemia were insulin use in pregnancy (HR=3.4) and Asian ethnic roots (HR=2.4). Other studies support the increased incidence of T2DM in women of Asian ascent [18], whereas some have found contradictory results. In a Southern California study by Xiang et al. in 13,000 women with GDM and 65,000 controls, the ORs of diabetes for women after GDM were 6.5 in non-Hispanic white, 7.7 in Hispanic, 9.9 in black and 6.3 in Asian/Pacific Islanders after adjustment for parity, maternal education and comorbidity [19]. The HR of diabetes for black women was 52% higher than that for non-Hispanic white women (p=0.032) and was lowest among Asians. The contradictory findings in women of Asian origin in the reported studies could be related to the study design, as many of these studies treated them as one racial group and their origin was not specified.

GDM and risk of hypertension

Women with a history of GDM have a higher risk of developing hypertension. In the United States, a study by Carr et al. with data covering up to 30 years postpartum found that the group of women with a history of GDM had a higher prevalence of hypertension (47% vs 37%, OR=1.88), were prescribed more antihypertensive drugs (45% vs 35%) and were diagnosed at a younger age (40 vs 48 years) [21]. These differences remained significant after adjusting for age, presence of menopause and ethnicity (differentiating between Caucasians, African Americans, Latinas and others). In this study, the authors did not describe ethnic differences in the development of hypertension.

The increased prevalence of preeclampsia in women with GDM and of postpartum hypertension in women who had preeclampsia is also well established [22,23], as well as the effect of ethnicity on the development of preeclampsia [24]. Bentley et al. carried out the first study of the impact of ethnicity on the development of hypertension in women with a history of GDM, differentiating between white, black, Asian and Hispanic women but without analysing any subgroups [25]. They observed that women with GDM were 2.45 times more likely to develop hypertension compared to women without GDM; the relationship between GDM and hypertension was attenuated after adjusting for age, ethnicity, parity, body mass index, systolic blood pressure during pregnancy, pregnancy weight gain and preeclampsia, but remained significant. With respect to ethnicity and the development of hypertension, analysing women with GDM and controls together, Black and Hispanic women had higher risk (HR=3.28 and 1.69, respectively) and Asian women had lower risk (HR=0.32), compared with White women. Comparing women with a history of GDM to controls, White and Hispanic women in the GDM group were at significantly higher risk of hypertension (HR=2.5 and 3.4, respectively) but no differences in risk were observed in Black and Asian women [25].

In the Nurses' Health Study II, including 25,300 women of mixed ethnicity with a 16-year postpartum follow-up, 5.6% developed GDM and 1% developed T2DM. Women with GDM who developed T2DM had an HR of 2.55 for hypertension incidence, compared to those with neither of these diagnoses. There was no evidence of effect modification by race and ethnicity [26].

GDM and risk of dyslipidaemia

Several studies have demonstrated a more adverse lipid profile in women with a history of GDM. A study carried out in the United States in Caucasian women with previous GDM found significantly higher concentrations of total cholesterol, triglycerides and low-density lipoproteins (LDL) in women with GDM compared with controls at 6 years postpartum [27]. In women with a history of GDM and a family history of T2DM, Carr et al. found a higher prevalence of dyslipidaemia (34% vs 26%), greater use of cholesterol-lowering drugs (18% vs 14%), specifically statins (15% vs 10%), and diagnosis at a younger age (48 years vs 52 years), than controls. This association remained significant after adjusting for age, presence of menopause and ethnic group [21]. In a Canadian population mainly including Caucasian women, Retnakaran et al. reported a graded relationship between glucose tolerance status in pregnancy and postpartum lipid levels. Compared with their peers, women with GDM and glucose intolerance in pregnancy had a more atherogenic lipid profile by 3 months postpartum, characterized by increased LDL and apolipoprotein B [28]. Nevertheless, other authors have found no differences in LDL cholesterol between women with GDM and those with normal gestational glucose tolerance in the first 3 years postpartum [29,30]. None of these studies, however, evaluated ethnic differences in the prevalence of lipid disorders in these women.

Impact of obesity on GDM

Obesity, and specifically central obesity, is a decisive factor in the increased vascular risk of women with a history of GDM. Women with obesity have more insulin resistance, which has been related with endothelial dysfunction. The cut-off value (80 cm) for waist circumference established by the International Diabetes Federation is the same for women in all ethnic groups [4]. Nevertheless, the 2015 recommendations of the American Diabetes Association adjusted the body mass index value for the Asian population, defining the cut-off for overweight as 23 kg/m2 because this population had a higher risk of diabetes with lower levels of body mass index than the general population [31].

Prepregnancy weight is a vitally important factor in determining the risk of developing postpartum T2DM in very diverse ethnic groups, as pointed out by Bellamy, Kim and Carson, in their respective systematic reviews/meta-analyses [2,3,11]. These results coincide with studies carried out in the Spanish population in Caucasian women [12,13]. Increased body mass index before pregnancy has been related with poor carbohydrates tolerance during pregnancy and with a more atherogenic lipid profile postpartum [27].

Inversely, women with previous GDM are more likely to have central obesity than normoglycaemic age-matched controls. In a study of women with a history of GDM compared with controls over 11 postpartum years, obesity rates in both groups of women were high, 40% and 37%, respectively. However, women with GDM had a higher prevalence of central obesity, defined as a waist-hip ratio of 0.85 or more, during follow-up than the controls [32]. Moreover, obesity is an important risk factor for the development of other components of the metabolic syndrome. In a group of Danish women with previous GDM, the combination of obesity and previous GDM increased the

prevalence of the metabolic syndrome more than 7-fold, compared with normal-weight women with prior GDM [33].

Risk of metabolic syndrome

Metabolic syndrome, like GDM, identifies patients at risk of developing T2DM and cardiovascular disease [34-36]. Figure 1 depicts prevalence of metabolic syndrome in different ethnic population during follow-up of women with previous GDM. In a Danish population with a 10-year postpartum follow-up, Lauenborg et al. described a prevalence of the metabolic syndrome that was three times higher in the prior GDM group, compared with the control group [33]. In a recent study in an Indian population, Karoli et al. reported 64% prevalence of the metabolic syndrome 1-5 years postpartum in women with a history of GDM, compared to 10% in the control group. Waist circumference exceeded 80 cm in 82% of women with previous GDM and in 44% of controls, prevalence of hypertension was 54% vs 12% and hypertriglyceridaemia 52% vs 10%, respectively [37]. Along the same lines, but with the limitation that the study was carried out 3 months postpartum, in a Canadian population with 70% of women of Caucasian origin and 10% of Asian ascent, the authors showed increasing prevalence of metabolic syndrome related to poor carbohydrates tolerance during pregnancy in 10%, 17% and 20% of women with normal tolerance, intolerance and a diagnosis of GDM, respectively. Non-Caucasian ethnicity was a predictor for postpartum metabolic syndrome [38]. This result agrees with the findings in an Iranian population at 23 months postpartum of 20% prevalence of metabolic syndrome in 110 women with previous GDM [39]. Kousta et al. presented data showing that women with GDM had 37% global incidence of metabolic syndrome at 20 months postpartum, with a higher incidence in Indo-Asians (49%) and African-Caribbeans (43%), compared to Europeans (37%) [40]. In a cohort of women with mixed ethnicity having a history of GDM and family history of T2DM, Carr et al. found a higher risk of metabolic syndrome (OR= 3.28), adjusted for age, presence of menopause and ethnicity, when compared to their peers. By ethnicity, the OR was 3.35 in Caucasians, 3.63 in African Americans and 2.82 in Latinas [21]. In a Turkish population, Akinci et al. observed that predictors of metabolic syndrome at 40 months postpartum in univariate analysis included prepregnancy obesity, weight gain during the pregnancy and basal glucose level in the oral tolerance test during pregnancy, with prevalence between 15% and 26% depending on the criteria applied [41].
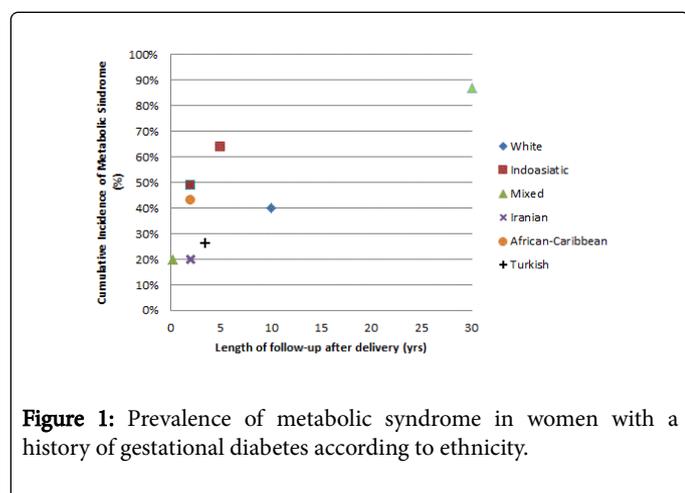

Figure 1: Prevalence of metabolic syndrome in women with a history of gestational diabetes according to ethnicity.

Vascular disease

In recent years, certain vascular parameters such as endothelial dysfunction and carotid intima-media thickness have acquired greater importance as they became recognized as vicarious markers of coronary arteriosclerosis and cardiovascular events [42]. A meta-analysis by Li et al. included 14 studies and 2,000 patients of mixed origin and showed a relationship between GDM and greater carotid intima-media thickness, an association that exists at the time of pregnancy and is affected by body mass index [43].

In a Canadian population including 70% Caucasian women, Shah et al. calculated a relative risk of cardiovascular episodes of 1.7 (95% CI: 1.08-2.69) in patients with previous GDM. Nonetheless, this risk was attenuated when adjusted for those patients who had developed T2DM; in other words, increased cardiovascular risk in this cohort was attributed mainly to the development of T2DM, not to the history of GDM [44]. In contrast, Carr et al. reported an increased risk of cardiovascular disease and coronary heart disease (OR=1.85 and 1.58, respectively) in a population with history of GDM and family history of diabetes that remained significantly high after adjusting for the presence of metabolic syndrome (OR=1.74) or T2DM (OR=1.56) [21]. The same authors stratified their results by ethnicity and found an OR of 1.62 for Caucasian Americans, 1.27 for African Americans and 2.91 for Hispanic Americans.

Not only is a history of GDM associated with cardiovascular disease; in addition, some studies have found an association with a greater risk of microvascular disease. In a population-based study in Israel, women with previous GDM had a higher risk (OR=2.3) of renal morbidity, compared to controls [45].

Conclusion

A history of at least one episode of GDM confers added vascular risk, which is greater in women who will develop T2DM but is also present in women whose glucose metabolism was unaltered during postpartum follow-up [46-48]. These women are at risk of developing not only T2DM but also metabolic syndrome, hypertension, dyslipidaemia and vascular disease, both subclinical and established; in general, however, global risk is greater in those who develop T2DM.

Although some authors maintain that post-GDM risk of T2DM does not vary by ethnic group [2], most report that Asian ethnicity is associated with greater risk of postpartum dysglycaemia. Specifically, Asian and African American women would have greater risk of T2DM [15,18,19] and Caucasians and Hispanics greater risk of arterial hypertension [25].

Given that women with ethnic origins in South Asia (India, Sri Lanka and Pakistan) have greater risk of GDM than those from southeast Asia, and that more cardiovascular events have been reported in these minority ethnic groups than in Chinese and European populations, after adjusting for risk factors and for the degree of atherosclerosis, it appears that genetic factors favour thrombotic phenomena [49]. Therefore, we can conclude that not all ethnic groups have the same vascular risk after an episode of GDM. There is a need for stricter control and follow-up of pregnant women with GDM in order to identify and intervene early in those risk factors that constitute the metabolic syndrome.

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