

# The Metabolic Syndrome in Offspring of Women with a Family History of Early Onset Type 2 Diabetes Mellitus Who Developed Gestational Diabetes Mellitus

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**Abstract Objective:** To evaluate for the metabolic syndrome (MS) in offspring of women with family history of early onset type 2 diabetes mellitus (T2DM) who developed gestational diabetes mellitus (GDM) using as controls offspring of women with no family history of diabetes and normal glucose tolerance (NGT). **Methods:** Anthropometric and biochemical measurements were evaluated for 30 offspring age 10-16 years of women with family history of early onset T2DM who developed GDM. Obstetrical records of these mothers were also noted. Thirty offspring of women (30) with NGT and no family history of diabetes served as controls. Measurements included: Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), fasting and postprandial glucose, insulin, waist circumference, weight and height. For analyses, MS was defined as  $\geq 3$  of 4 features: glucose intolerance, dyslipidemia, obesity and hypertension in the childhood/adolescence criteria as recommended by the National Cholesterol Education Program Adult Treatment Panel Third (NCEP-ATP III) modified standard. Cox regression analysis was used to determine the independent hazard (risk) of developing MS attributable to GDM with a family history of early onset T2DM. Results: Offspring of women with GDM and family history of early onset T2DM had significantly more ( $\geq 2$ ,  $p < 0.05$ ) features of MS than offspring of women with NGT and no family history of diabetes. Thirty percent (30.0%), 29.5% and 39.0% of the offspring of these GDM women had glucose intolerance, obesity and dyslipidemia respectively. These offspring had a hazard of 3.33 (95% CI: 2.12-9.15) of having MS compared to offspring of women with NGT and no family history of diabetes. **Conclusion:** Offspring of women with GDM and family history of early onset T2DM are at increased risk for MS.

**Keywords:** early onset type 2 diabetes, offspring, gestational diabetes

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## 1. Introduction

Glucose normally crosses the placenta however there is usually an increased flux of glucose from the maternal circulation into the fetal circulation in women with in GDM or diabetes in pregnancy. [1] This induces an increase in fetal insulin production because maternal insulin does not cross the placenta. Increased maternal glucose levels induce fetal fat deposition and skeletal development [2] resulting in large for gestational age (LGA) or macrosomic babies. [3] Research indicates that LGA babies are at risk for a cluster of deranged metabolic conditions such as obesity, dyslipidaemia, hyperglycemia and hypertension during childhood. [3] Not only LGA babies of mothers with GDM are at risk for these conditions but disturbances of lipoprotein metabolism with hypercholesterolemia have been reported in appropriate for gestational age (AGA) offspring. [4] Children of mothers who had GDM have lower HDL-C and higher TG levels than children from mothers with NGT. [5] Exposure to maternal diabetes also correlates with increased blood

pressure in offspring. [6] Women who develop GDM therefore present a metabolically toxic intrauterine environment which puts their children at risk for the development of chronic conditions including derangement in metabolism or the metabolic syndrome.

Metabolic syndrome in adults has been classified as the clustering of some dangerous risk factors such as hyperglycemia, dyslipidemia and hypertension which predisposes an individual to diabetes and coronary heart disease. [7,8] Clustering of these risk factors have also been found in children however there are contrasting views on which of these factors should be included and how these factors should be scaled for the diagnosis of MS in children [9,10,11]. Regardless of the derangement or scale there is still compelling evidence that the intrauterine environment in GDM pregnancy predisposes the index child to forms of MS. [1,5] Metabolic syndrome also has a genetic component and occurs commonly in some families [12].

Early onset type 2 diabetes mellitus (T2DM) is defined as having a family history of diabetes mellitus (DM) in multi-generations with  $\geq 2$  first degree relatives diagnosed with T2DM before age 35 years and DM only on the

maternal or paternal side of the family. [13] It was hypothesized that the hazard of MS in offspring of GDM women with a family history of early onset T2DM would be raised above that of offspring of women with no family history of diabetes and NGT because of GDM and strong multigenerational family history of early onset T2DM. Other studies looked at MS in children and adolescents. [10,11] There is however a dearth of information on MS in adolescents who are offspring of women with familial history of early onset T2DM who first developed diabetes pregnancy with the index offspring. The main objective of the study was therefore to determine whether the risk for MS was raised in offspring of women with a family history of early onset T2DM who developed GDM.

## 2. Methods

A cohort study was carried out in 2012 on offspring of women with family history of early T2DM who developed GDM during pregnancy with the studied offspring. This was a follow up of an earlier study on the genomic scan of families with early onset T2DM. [14] The study sought to find out if familial history of early onset T2DM in women who developed GDM during pregnancy with the index child increases the risk of that offspring developing MS. Familial history of early onset T2DM was defined as used by Doria et al (1999). Offspring of women with NGT and no family history of diabetes who were born at the same antenatal facility during birth of the cohort served as controls. The protocol was approved by the hospital's Institution Review Board at the University Hospital of the West Indies (UHWI), Jamaica. Written informed consent was obtained from mother and assent was obtained from recruited offspring. Ethical standards were followed in accordance with the Declaration of Helsinki revised in Brazil 2013. Participating offspring and mothers were interviewed by a research student.

Exclusion criteria for offspring included: offspring of multifetal gestations, congenital anomalies and preterm infants (<37 wk gestation). Offspring of mothers who had abnormal pre-gravid weight gain, chronic diseases, and co-morbidities existing with GDM prior to recruitment to the study were also excluded. Siblings were also excluded.

Inclusion criteria: The offspring of women who had registered for ante-natal care at the University Hospital of the West Indies from 1994 through 2004.

Consent was given by mothers to have delivery records and docket examined for data retrieval. The mothers' obstetrical records were reviewed. Maternal height and pre-gravid weight were attained from the recorded history on the first ante-natal visit to the clinic. Maternal pre-gravid weight was defined as a pre-gravid BMI, defined as weight (in kg)/height squared (in m). Overweight was defined as a BMI >25 kg/m<sup>2</sup>, normal as BMI <25 kg/m<sup>2</sup> and underweight as BMI <18.5kg/m<sup>2</sup>. Maternal weight gain was assessed from the docket as the weight at delivery minus the pre-gravid weight. Maternal age at delivery, parity, glucose tolerance and tobacco and alcohol use were obtained from the history at the time of delivery and a review of the maternal antenatal record. The antenatal records were also reviewed for results of fasting glucose, insulin, total cholesterol (TC), HDL-C, TG and postprandial glucose just prior to delivery (<7 days before

delivery). Insulin resistance [15] prior to delivery was also calculated from data in the record.

The follow-up studies in the children were performed by contacting the mothers in 2012 after a review of dockets and having the follow-up studies performed on offspring who were between 10 and 16 years old. Thirty (30) offspring age 10-16 years of women with family history of early onset T2DM who had GDM along with 30 offspring of women with no family history and NGT were recruited. Offspring were weighed and had height taken on a calibrated weight/height scale (Detecto, USA). Appropriate percentiles for weight and height were assigned by using the Centers for Disease Control and Prevention (CDC) criteria. [16] Waist circumference was measured and appropriate percentiles were also assigned.<sup>16</sup> Blood pressure with a calibrated childhood cuff was determined in three sequential measurements and the average recorded. [17] Venous blood was taken for fasting glucose, insulin, TC, HDL, TG and postprandial glucose. Insulin resistance was also calculated. 14 The components of MS for this study were defined as (i) fasting glucose level >110 mg/dL or 6.1mmol/l (ii) waist circumference ≥ 90th for age, (iii) diastolic or systolic blood pressure >90th percentile for age, (iv) HDL-C level ≤10<sup>th</sup> percentile for age or TG >90th percentile for age. [9]

### 2.1. Laboratory Analysis

Plasma glucose was measured by the glucose oxidase method (Sigma Diagnostics, Livonia,MI, USA). The TC and TG were measured in the RA-1000 autoanalyser (Technicon Instruments Corporation, New York, USA). HDL-C was measured in the RA-1000 autoanalyser (Technicon Instruments Corporation, New York, USA) after precipitating out the apo-B-containing lipoproteins. Fasting serum insulin was measured by the sandwich immunoassay method (Roche Diagnostics, Indianapolis, IN, USA). Insulin resistance (HOMA-R) using the homeostasis model assessment was calculated as  $\text{insulin}_0 (\mu\text{IU/mL}) \times \text{fasting glucose}_0 (\text{mmol/L}) / 22.5$ . [15]

### 2.2. Statistical Analysis

Statistical analyses were performed by using a Mann-Whitney *U* test to compare the means of the 2 groups depending on the normalcy of the distribution. Comparisons of non-continuous data were done using a chi-square test. ANOVA for parametric data and a Kruskal-Wallis test for nonparametric data were used to differentiate between the various percentiles. Logistic and multiple regression analyses were used to predict the outcome of interest. We included maternal obstetrical data, and neonatal birth data to best determine which combination of factors best modeled the risk of metabolic dysfunction in the offspring. Data are expressed as means ± SDs, and a *P* value <0.05 was considered significant. Statistical analyses were performed by using SSPS version 20 (IBM, USA).

## 3. Results

Of the 60 offspring enrolled in the study, 7(11.7 %) were small-for-gestational age (SGA), that is less than the 10th percentile; 45(75.0 %) were appropriate weight for

gestational age (AGA) that is within the 10th to the 90th percentiles and 8 (13.3%) were large-for-gestational age (LGA),  $\geq 90$ th percentile.<sup>16</sup> Of the 30 offspring of mothers with GDM and family history, 1(3.3%) was SGA, 24 (80%) were AGA and 5 (16.7) were LGA. Of the 30 offspring of women with NGT, 6 (20.0%) were SGA, 21(70%) were AGA and 3 (10.0%) were LGA.

The offspring of women with family history of early onset T2DM and GDM weighed significantly more ( $P<0.05$ ) than offspring of the women with no family history of diabetes and NGT. The offspring of women with family history of early onset T2DM and GDM also

had significantly larger waist circumference than offspring of women with no family history of diabetes and NGT. Approximately 10% had waist circumference  $>95$  percentile for age and 2% had waist circumference  $>97$  percentile. [16]

Fasting glucose, postprandial glucose, fasting insulin, HOMA-IR and TC and TG were significantly lower ( $P<0.05$ ) in the offspring of women with no family history of diabetes who had NGT compared to the offspring of women GDM and family history of early onset T2DM (See Table 1).

**Table 1. Anthropometric and metabolic parameters for two groups: Offspring of NGT women without family history of diabetes (ONGT) and offspring of women with family history of early onset T2DM who developed GDM (OGDM)**

	ONGT (n=30)	OGDM (n=30)	Pvalue
Weight percentile	60.9 $\pm$ 26.4	64.1 $\pm$ 32.9	
Age (yrs)	12.0 $\pm$ 3.7	11.6 $\pm$ 2.8	
Male/female (n)	14/16	15/15	
Weight (kg)	31.0 $\pm$ 8.1	33.5 $\pm$ 13.6	
Height (cm)	130.6 $\pm$ 12.9	133.2 $\pm$ 13.9	
Waist Circumference (mm)	60.2 $\pm$ 8.7	63.1 $\pm$ 10.5	
Systolic BP (mm Hg)	108 $\pm$ 12	110 $\pm$ 11	
Diastolic BP (mm Hg)	60 $\pm$ 7	60 $\pm$ 9	
Fasting glucose (mmol/L)	5.0 $\pm$ 2.7	6.2 $\pm$ 5.8	
Postprandial glucose (mmol/L)	6.2 $\pm$ 2.4	6.8 $\pm$ 5.4	
Fasting Insulin (pmol/L)	11.0 $\pm$ 2.5	12.0 $\pm$ 3.9	
HOMA-IR	1.9 $\pm$ 0.8	2.5 $\pm$ 1.4	
Total Cholesterol (mmol/L)	3.8 $\pm$ 0.4	4.2 $\pm$ 0.5	
Triglyceride (mmol/L)	0.9 $\pm$ 0.3	1.1 $\pm$ 0.7	
HDL cholesterol (mmol/L)	1.2 $\pm$ 0.3	1.1 $\pm$ 0.2	

The women with family history of early onset T2DM and GDM had significantly higher ( $P<0.05$ ) pre-gravid weight, pre-gravid BMI and weight gain during pregnancy

and were significantly less ( $P<0.01$ ) multiparous compared to women with no family history who had NGT (see Table 2).

**Table 2. Maternal demographics of women whose offspring were evaluated for the metabolic syndrome (MS)**

	NGT (n=30)	GDM (n=30)	P<value
Age at delivery (years)	30.2 $\pm$ 8.1	30.5 $\pm$ 13.2	0.10
Height (cm)	164.0 $\pm$ 12.1	167.2 $\pm$ 14.1	0.09
Pre-gravid weight (cm)	64.5 $\pm$ 10.1	67.2 $\pm$ 16.2	0.05
Pre-gravid BMI (kg/m <sup>2</sup> )	23.1 $\pm$ 5.1	23.9 $\pm$ 6.2	0.05
Weight gain (kg)	11.1 $\pm$ 3.1	12.4 $\pm$ 2.9	0.04
Pre-eclampsia (n)	0	1	0.09
Parity (n)			
0-1	9	12	0.01
>1	13	7	0.01
Fasting glucose (mmol/L)	5.2 $\pm$ 1.9	6.1 $\pm$ 2.8	0.01
Postprandial glucose (mmol/L)	6.8 $\pm$ 2.1	7.5 $\pm$ 1.9	0.05
Fasting Insulin (pmol/L)	11 $\pm$ 2.5	12 $\pm$ 3.9	0.04
HOMA-IR	1.8 $\pm$ 0.8	3.9 $\pm$ 1.4	0.02
Total Cholesterol (mmol/L)	4.9 $\pm$ 0.4	5.2 $\pm$ 0.8	0.06
Triglyceride (mmol/L)	1.0 $\pm$ 0.3	1.7 $\pm$ 0.6	0.01
HDL cholesterol (mmol/L)	1.2 $\pm$ 0.3	1.2 $\pm$ 0.2	0.99
Smoke (yes/no)	7/15	3/16	0.05
Drink alcohol (yes/no)	3/19	1/18	0.09

$P<0.05$  indicates statistical significant difference between groups.

Fasting and postprandial glucose, fasting insulin, HOMA-IR and TG levels were significantly higher ( $P<0.05$ ) in women with family history of early T2DM who developed GDM. HDL-C levels were similar (1.2  $\pm$ 0.3mmol/l versus 1.2  $\pm$ 0.2mmol/l) in women with family history of early onset T2DM who developed GDM and women with no family history of diabetes and NGT. Women who had no family history of diabetes and NGT smoked significantly more ( $P<0.05$ ) and tend to drink

more alcohol though not significantly so ( $P>0.09$ ) than women with family history of early onset T2DM who developed GDM (see Table 2).

## 4. Discussion

Many studies have shown that the diabetic intrauterine environment in GDM pregnancies has long term effects on

lipid, glucose and blood pressure in offspring. [3,5] Family history of diabetes has also shown an independent association with MS.[7] One study found that early treatment of women with mild GDM did not translate into a reduction in metabolic dysfunction in offspring.[18] Metabolic syndrome in childhood can translate into atherosclerotic processes in later life. [19] The Bogalusa study found that TC and blood pressure in children at risk for MS correlated with infiltration of foam cells and lipids in the arterial intima layer which then evolved into atherosclerotic plaques with fibrosis and necrosis. [20] Early identification of features of MS in children is therefore essential to reduce mortality and morbidity rates.

The offspring of women with a family history of early onset T2DM and GDM had significantly lower HDL-C and higher TG levels than offspring of women without family history of diabetes and NGT in pregnancy. Diabetes in pregnancy usually precipitates fatty streak formation in human fetal aortas which causes intimal accumulation of low density lipoprotein [21] and therefore less HDL-C for the cholesterol concentration. The offspring of the women with GDM and family history also had higher fasting and postprandial glucose values. Glucose values may have impacted the glycation of HDL-C in these offspring which happens when there is some dysfunction in lipid metabolism, a manifestation is often seen by an increase in TG level. [22] The TG values were significantly higher ( $P<0.05$ ) and HDL-C values significantly lower ( $P<0.04$ ) in the offspring of women with GDM and family history of early onset T2DM compared to offspring of women who had no family history of diabetes and NGT. Other studies that analyzed MS in adolescents and college aged offspring of women with GDM have also noted a relationship between HDL-C and TG. Lower HDL-C levels in the offspring of women with GDM in these studies were associated with increases in TG levels. [23,24]

The study reported that 30% of the offspring of women who had family history of early onset T2DM and GDM presented with obesity as compared to 10% of offspring of women who had no family history of diabetes and NGT. Waist circumferences were significantly larger for offspring of women with GDM and family history of early onset T2DM. Fifty percent (50%) of the approximately 30% of the obese offspring of the GDM women had waist circumference  $> 95^{\text{th}}$  percentile for age. One study that perused the literature for the relationship between GDM and childhood obesity reported crude odd ratios of 0.7 to 6.3%. [25] GDM puts the offspring at increased risk of developing obesity in childhood. Family history of T2DM may also add to that risk of obesity in childhood [26] and this may have accounted for why obesity was 3 times more common in the offspring of women with GDM and family history of early onset T2DM compared to the offspring of women with no family history of diabetes and NGT. Women with GDM usually have a family history of T2DM [26] not necessarily early onset T2DM. [13] One study observed marked impairment in fetal insulin sensitivity in diabetic pregnancies independent of family history of diabetes and suggested a mother baby metabolic programming cycle. [27] programming may have been multi-generational since the diabetes is autosomal and was passed down on the maternal side. [13]

It was noted in the current study that 10% of the offspring of the women with no family history of diabetes and NGT were obese. There seems to be a link between LGA and obesity in childhood as reported in other studies. [1,3,5] Eighty percent (4/5) of the LGA babies of the GDM mothers showed obesity in childhood and 66% ( 2/3 ) of the LGA babies of the mothers with NGT displayed obesity in childhood. No adjustment was made for maternal pre-pregnancy BMI or weight gain during pregnancy as only women with normal pre-pregnancy BMI were included in the study. The study cohort was monitored tightly to ensure that weight gain during pregnancy was within the normal range. There was no significant difference in maternal age between the women without family history of diabetes and NGT and those with GDM and family history of early onset T2DM. Maternal age, pre-gravid weight, weight gain in pregnancy and parity have been associated with increased risk for obesity in offspring. [28] The women without family history of diabetes and NGT had significantly more children than those with GDM. Childhood obesity linked to maternal age, pre-gravid weight, weight gain in pregnancy and parity were therefore ruled out in this study.

Conflicting data have been reported on the relationship between GDM and blood pressure in offspring. One study found no significant relationship between systolic blood pressure and GDM in 17 years old offspring. [29] A retrospective study of Pima Indians in contrast found that systolic blood pressure was significantly increased in 7-11 years old offspring of women with GDM. [30] In another study the systolic and mean arterial blood pressure of offspring showed a significant association with GDM. [31] No relationship has been found between GDM women with family history of early onset T2DM and blood pressure in their offspring in this study.

One study reported that intrauterine hyperglycemia induced impaired glucose tolerance in F1 offspring. [32] Glucose intolerance was present in 30% of offspring of mothers with GDM and family history of early onset T2DM. The elevated fasting glucose values in the offspring of women with GDM in this study were consistent with values noted in other studies as the offspring of women with GDM generally have higher glucose values. [33,34]

The women and their offspring including controls (no history of diabetes and NGT in pregnancy) in this study were predominately of Afro-Caribbean descent. Ethnicity has been associated with MS in offspring of minority groups in the USA. [35] No association was found in this study between ethnicity and MS because  $<2$  of the 4 features that define MS (glucose intolerance, dyslipidemia, measures of obesity and hypertension) was noted in controls who were also of Afro-Caribbean descent.

The offspring of women with GDM and a family history of early onset T2DM were found to be of increased risk of MS with hazard of 3.33 (95% CI: 2.12-9.18). A family history of T2DM was associated with higher levels of insulin resistance in children. [36] Although the offspring of women with GDM and family history of early onset T2DM were trending towards an insulin resistance state, they did not fit the criteria for the definition of insulin resistance  $>3.16$  as used in another study. [37] Their mothers with family history of early onset T2DM and GDM showed some level of insulin resistance (3.9

$\pm 1.4$ ) and had significantly higher fasting glucose and triglyceride values ( $P < 0.01$ ) than mothers with no family history of diabetes and NGT. The results showed that GDM with a family history of early onset T2DM puts offspring at increased risk for MS. There seems to be some sort of intrauterine milieu. The possibly pathophysiology may include nutrient alterations and fetal teratogenesis. [38] Many women with GDM present with a family history of T2DM. [1] One could not by the design of this study measure the impact of the history early onset T2DM of the GDM women on the MS rate in their offspring however in another study family history of T2DM had no direct impact on MS rate in normal and overweight Brazilian children. [36] Conversely another study reported an adjusted odds ratio of 3.53, 95%CI: 1.33, 9.31 for MS in offspring of GDM women in a general population cohort. [28] Yet another study by Malcolm et al concluded that school age children of mothers with GDM are at risks for MS even if the population has a low risk for diabetes. [39] The hazard risk of 3.33 is close to 3.53 reported in another study. [28] The association between GDM and family history of early onset T2DM on MS rate in the offspring may be multifactorial possibly including genetic and pre and post natal interactions. The offspring of women with GDM and family of early T2DM in this study is at increased risk for MS how much family history of early onset T2DM in GDM adds to the risk in offspring is however debatable.

The study had some limitations. We would have liked to have included offspring of women with family history of early onset T2DM who did not develop GDM and offspring of women having no family who developed GDM. Only 3 offspring of women with family history of early onset T2DM who did not developed GDM were identified, however the mothers and children did not wish to participate in the study. Most studies have reported that women with GDM usually have a family history of diabetes. [6,7] Our study reported on women with GDM and early onset T2DM, which is an atypical form of T2DM. [13] We did not examine the effects of exercise and diet on the manifestations of MS in offspring. However most if not all the study participants including the offspring of women with NGT were from the same social class and generally shop for food in the market or local shops in the metropolis. We therefore assumed dietary patterns were similar in both GDMs and controls.

Despite these limitations, our findings are relevant as the findings contribute to the understanding of the risk factors and features of MS among offspring of GDM women with a family history of early onset T2DM. This is the first study of its kind to explore MS in the offspring of women with long standing familial history of diabetes who first become affected during the index pregnancy.

## Statement of Competing Interests

None declared

## List of Abbreviations

HDL-C: High Density Lipoproteins  
LDL-C: Low Density Lipoproteins

TC-C: Total Cholesterol

TG: Triglycerides

GDM: Gestational diabetes mellitus

MS: Metabolic syndrome

T2DM: Type 2 diabetes mellitus

OGDM: Offspring of gestational diabetes mellitus

ONGT: offspring of normal glucose tolerance

HOMA-IR: Insulin Resistance

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